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CHEMICAL CARCINOGENESIS

Azo Dyes, Aryl Amines, and Related Compounds

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ANILINES AND EXTENDED ANILINES

1. CHEMICAL CARCINOGENS AND THEIR RELEVANCE FOR CANCER INDUCTION IN HUMANS WITH SPECIAL REFERENCE TO DERMATOLOGICAL PROBLEMS.

Schmahl D, Bertram B
Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany

Derm Beruf Umwelt; 29(3):75-79 1981

Cancer induction by dermatologic medication has been nearly eliminated since As is no longer used for treatment of skin conditions. There is, however, a controversy about the cancerogenic effect of aniline pigments. These chemicals were replaced by substitutes (Castellani's soln) some decades ago. The treatment of large wounds with amine containing powder

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during World War II has caused liver necrosis and cirrhosis. (10 Refs) (In GER)

2. DAMAGE TO LIVER, KIDNEY, SPLEEN AND BONE MARROW DNA IN RATS AND MICE FOLLOWING TREATMENT WITH COMMERCIAL AND DISTILLED ANILINE (MEETING ABSTRACT).

Russo P, Pala M, Taningher M, Parodi S, Santi L
No affiliation given
Tumori; 67(2,SupplA):132 1981

The compound, suspended in carboxymethylcellulose, was administered to male Sprague-Dawley rats and male Swiss mice by a single ip injection in doses of 53, 105, 210, and 840 mg/kg and sacrificed 4 hr after treatment, and in a single dose of 210 mg/kg with sacrifice 24, 48, 72, and 120 hr later. Dose-dependent DNA damage was clearly demonstrated in the liver with a max at the 210 mg/kg dose. Damage plateaus at doses higher than 210 mg/kg probably because of saturation of the metabolic systems. DNA damage was also evident in the kidneys at the 210 mg/kg dose. No damage was found in the spleen or bone marrow, however. At 210 mg/kg the distilled product also induced DNA fragmentation identical to the damage induced by the commercial compound. The results expressed as the elution constant: K (median value) were as follows: (a + means a statistically significant difference from the controls) controls liver, K, 0.0221; 53 mg/kg, K, 0.0196; 105 mg/kg, K, 0.0315 (+); 210 mg/kg, K, 0.0446 (+); 210 mg/kg (distilled), K, 0.0503 (+); 840 mg/kg, K, 0.0548 (+); 210 mg/kg, 24 hr, K, 0.0432 (+); 210 mg/kg, 48 hr, K, 0.0302; 210 mg/kg, 72 hr, K, 0.0149; controls, kidney, K, 0.0564; 210 mg/kg, K, 0.1130 (+). (no Refs) (In ITA)

3. MUTAGENICITY AND RAT-LIVER S9 DEMETHYLATION KINETICS OF N-NITROSOMETHYLANILINE AND ITS RING-SUBSTITUTED DERIVATIVES.

Kroeger-Koepke MB, Andrews AW, Kupper RJ, Koepke SR, Michejda CJ
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Mutat Res; 89(4):255-267 1981

Mutagenicity of N-nitrosomethylaniline (NMA) and its ring-substituted derivatives was investigated using Ames Salmonella typhimurium tester strains. The standard assay involved the application of NMA to strain TA100 (most sensitive toward substituted NMAs) at concentrations ranging from 1-1,000 ug/plate. Neither the parent NMA nor most of its substitutes showed any effect on the tested strains. The same was true in both the presence or absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. In order to test possible activation or deactivation of the metabolites, the protein concentration of S9 was varied from 0.2 mg/plate to 6.4 mg/plate. The series also included a liquid suspension variant of the Ames assay using all Ames strains. In both test series (various protein concentrations and liquid suspension) the nonmutagenicity of NMA was confirmed. Some ring-substituted derivatives, however, showed a positive mutagenic response (for example, p-NO2, m-Br, m-NO2). (17 Refs)

4. SCE INDUCTION IN BONE MARROW CELLS OF MICE AND DNA FRAGMENTATION IN RAT LIVER FOLLOWING TREATMENT WITH AURAMINE O AND 4-4 OXYDIANILINE (MEETING ABSTRACT).

Vecchio D, Russo P, Ottagio L, Parodi S, Santi L
No affiliation given
Tumori; 67(2,SupplA):58 1981

Tests of both auramine O and 4,4'-oxydianiline have demonstrated their capacity to both increase sister chromatid exchange (SCE) induced by them and their ability to fragment DNA by means of the alkaline elution technic. Doses of auramine O (7.5 mg/kg) and 4,4'-oxydianiline (75 mg/kg) were administered in a single dose ip to male Swiss mice. In the bone marrow metaphases examined, the increase in exchanges in the animals treated was statistically significant when compared to the controls (Mann-Whitney test) for auramine O, but not for 4,4'-oxydianiline. It should be stressed that the experiments have only been carried out in triplicate for the present reading 20 metaphases per animal: auramine O: 5.2 SCE/cell, p less than 0.03; 4,4'-oxydianiline: 4.6 SCE/cell, p less than 0.3; controls: 3.8 SCE/cell. Doses of auramine O (30 mg/kg) and 4,4'-oxydianiline (730 mg/kg) were administered in a single ip to male Sprague-Dawley rats sacrificed 4 and 24 hr after treatment. For both compounds alkaline fragmentation of DNA was statistically significant with respect to the controls 4 hr after treatment (experiments in sextuplicate, Mann-Whitney test). In the case of auramine O DNA damage was no longer demonstrable after 24 hr of treatment. K is an elution rate constant ml-1 (median value). Auramine O, 4 hr, K: 7.15 x 10(-2), p less than 0.002; 24 hr, K: 1.34 x 10(-2), p greater than 0.1; 4,4'-oxydianiline, 4 hr, K: 7.76 x 10(-2) p less than 0.002; 24 hr, K: 6.32 x 10(-2), p less than 0.002; controls, K: 2.10 x 10(-2). (no Refs) (In ITA)

5. SCE INDUCTION IN BONE MARROW CELLS OF MICE FOLLOWING TREATMENT WITH ANILINE (MEETING ABSTRACT).

Zunino A, Ottaggio L, Vecchio D, Parodi S, Santi L
Inst. Oncol. University - Genova, Genoa, Italy
Tumori; 67(2,SupplA):58 1981

We used sister chromatid exchange (SCE) (exchange between chromatid twins) to test the possible action of aniline at the genome level in vivo. Stepwise doses of aniline (61 mg/kg, 123 mg/kg, 210 mg/kg) were administered ip to male Swiss mice. The metaphases examined were from bone marrow. The increase in exchanges in mice treated with the max dose was highly significant (7.3 SCE/cell -3.7 SCE/cell, respectively; p.001) compared to the controls. The commercial product provided by Merck contained a small percentage of impurities and so in order to ascertain whether it was these impurities affecting the number of SCE we also tested aniline which had been distilled in our laboratory. The latter was administered in a single dose of 210 mg/kg: the increase in SCE over the controls still remained high and statistically significant. Linear regression analysis showed a highly significant relation between aniline dose and increase in SCE. (no Refs) (In ITA)

6. PREDICTIVE VALUE OF THE DNA ALKALINE ELUTION TEST IN EVALUATING THE ONCOGENIC RISK FROM AROMATIC AMINES (MEETING ABSTRACT).

Bolognesi C, Cesarone CF, Santi L
Istituto Scientifico per lo Studio e la Cura dei Tumori, Genoa, Italy
Tumori; 67(2,SupplA):56 1981

The alkaline elution method was used to determine changes in the DNA molecule induced by aromatic amines with different chemical structures administered in vivo. The chemical compounds (benzidine, 1-naphthylamine and 2-naphthylamine, aniline, 2-nitroaniline, 2,4-dinitroaniline, o-toluidine and p-toluidine) were injected ip into male CDI Swiss mice in doses equivalent to 2/3 of the LD50. A significant increase in alkaline elutability of DNA was demonstrated 4 hr after administration in the liver and kidneys of animals treated with benzidine, 1-and 2-naphthylamine, o- and p-toluidine. A negligible increase in DNA fragmentation in alkali was found for aniline and 2-nitroaniline, while the av elution constant for 2,4-dinitroaniline falls within the range of the controls. The good correlation with the long-term carcinogenicity tests is especially significant for o- and p-toluidine, compounds only recently shown to be mutagens following broader investigations with particular systems of metabolic activation. The different physico-chemical properties and above all different mechanisms of biotransformation of these molecules in vivo characterize the different toxic and oncogenic properties of this class of compounds. The short-term tests of carcinogenesis are greatly limited by the difficulties of experimentally reproducing the same metabolic conditions which occur during the process of cellular neoplastic transformation. The alkaline elution test in vivo allows the normal metabolic pathways for chemical compounds and, in spite of the difficulties involved in extrapolating the results obtained with rodents to man, added to other information, such as chemical structure and level of environmental exposure, it enables difinition of a correct toxicologic profile of chemical compounds. (no Refs) (In ITA)

7. VALIDATION OF A RADIOIMMUNOASSAY PROCEDURE FOR N,N'-DIACETYLBENZIDINE, A METABOLITE OF THE CHEMICAL CARCINOGEN BENZIDINE, IN URINE.

Johnson HJ, Cernosek SF, Gutierrez-Cernosek RM, Brown LL
Dept. Obstetrics and Gynecology, Univ. Texas Health Science Center, Dallas, TX, 75235
J Anal Toxicol; 5(4):157-161 1981

The development of a new radioimmunoassay procedure for the analysis of N,N'-diacetylbenzidine (N,N'-DAB) in urine is described. The assay is sensitive in the picomole range (av minimal detectable dose less than 10 picog and is specific for N,N'-DAB . Cross reactivity studies illustrate the lac k of significant cross reaction of antiserum with structurally related biphenyl derivatives. The procedure exhibits reproducibility and requires neither hydrolysis nor extraction of urine samples. Normal urine constituents contribute only a low level of nonspecific inhibition (av 0.52 nanog N,N'-DAB/ml urine). (8 Refs)

FLUORENAMINES: IN VIVO

8. GLYCOSYLATION REACTIONS AND TUMOR ESTABLISHMENT. MODULATION BY VITAMIN A.

Morre DJ, Creek KE, Morre DM, Richardson CL
Dept. Medicinal Chemistry, Purdue Cancer Center, Purdue Univ., West Lafayette, IN, 47907
Ann NY Acad Sci; 359:367-382 1981

The effect of retinyl acetate (RAC) on the course of experimental tumorigenesis was studied in weanling male inbred rats divided into three dietary groups: Deficient (no RAC), Adequate (4,000 IU/kg diet), and Excess (400,000 IU/kg diet). The transplantable hepatocellular carcinomas used were derived from tumors induced by acetylaminofluorene in CDF rats. A hepatoma line (H-2) metastatic to the lung was also employed. Vitamin A had little effect on tumor establishment when rats received sc injection of transplantable hepatoma cells on the initial day of diet. However, when rats were started on the dietary regimens 2 wk prior to tumor injection tumors were fewer and appeared later under conditions of either vitamin A deficiency or excess in some but not all experiments. In general, vitamin A showed no inhibitory effect on growth of tumors once established. In experiments with the metastatic hepatoma lines, the diet containing excess RAC (fed to rats starting 2 wk prior to tumor injection) prevented establishment of secondary tumor foci while 75% of rats fed adequate RAC showed pulmonary metastases. To relate loss of metastatic ability (ability for metastases to establish at distant sites), a study was made of the status of putative receptors for fibronectin. While dietary vitamin A little or no effect on total ganglioside content of liver or hepatocellular carcinomas, variations in ganglioside composition were observed. The vitamin A treated cells also showed reduced levels of bound fibronectin. Changes in neutral lipids related to vitamin A intake were also observed. The findings suggest involvement of higher gangliosides in the attachment of cells to a fibronectin-collagen complex. Alterations of fibronectin in relation to metastasis are discussed; analyses suggest that excess vitamin A may prevent the reappearance of fibronectin receptor gangliosides so that secondary tumor foci do not establish. (45 Refs)

9. RAPID DEVELOPMENT OF LARGE NUMBERS OF ALPHA-FETOPROTEIN-CONTAINING 'OVAL' CELLS IN THE LIVER OF RATS FED N-2-FLUORENYLACETAMIDE IN A CHOLINE-DEVOID DIET.

Sell S, Leffert HL, Shinozuka H, Lombardi B, Gochman N
Dept. Pathology, Univ. California San Diego Medical Sch., La Jolla, CA, 92093
Gan; 72(4):479-487 1981

Fischer rats, fed 0.05% w/w N-2-fluorenylacetamide in a choline-devoid diet for 2 wk, developed a massive infiltration of the liver by small 'oval' cells. This occured rapidly 1 wk after feeding the diet for 2 wk. All of the rats fed the choline-devoid diet died within 5 wk, with massive oval cell infiltration of the liver. Although similar changes occurred in rats fed N-2-fluorenylacetamide in a choline-supplemented diet, the degree was much less. In rats fed a choline-devoid diet without N-2-fluorenylacetamide, proliferation of hepatocytes, but not of oval cells, was observed. Because the carcinogen-enhancing effects of choline-devoid diets seem to exceed those of partial hepatectomy, such diets may work by causing changes distinct from those induced by partial hepatectomy. Many oval cells contain alpha-fetoprotein, and the rapid oval cell increase is associated with an exponential increase in serum alpha-fetoprotein concentration. These observations suggest that a cellular change, not an alteration of gene expression in parenchymal cells, is the primary cause of hyper-alphafetoproteinemia during the course of chemical carcinogenesis in rats. (Author abstract) (40 Refs)

10. INCREASE OF T CELLS IN THE LIVER DURING HEPATOCARCINOGENESIS WITH N-2-FLUORENYLACETAMIDE IN RATS.

Okita K, Ando K, Fukumoto Y, Miyazaki M, Tsubota W, Kodama T, Takemoto T
Dept. Internal Medicine, Yamaguchi Univ. Sch. Medicine, 1144 Kogushi, Ube 755, Japan
Gan; 72(4):610-614 1981

The localization of thymus-derived lymphocytes (T cells) was investigated in rat liver by the immunofluorescence method during hepatocarcinogenesis with N-2-fluorenylacetamide. In the early stage of carcinogenesis, the number of T cells never increased significantly in livers in which hyperplastic liver nodules (population I) were seen. On the other hand, in the late stage of carcinogenesis, T cells extensively invaded hyperplastic nodules (population II) as well as hepatomas. According to the concept of cell-mediated immunity, hyperplastic nodules in the late stage might have a neoantigen(s) which evokes the response of T cells. Therefore, it may be concluded that populations I and II are biologically distinct lesions in spite of their histological identity. (Author abstract) (13 Refs)

11. A NOVEL CELLULAR RETINOID-BINDING PROTEIN, F-TYPE, IN HEPATOCELLULAR CARCINOMA.

Muto Y, Omori M
First Dept. Internal Medicine, Gifu Univ. Sch. Medicine, Gifu City, Japan
Ann NY Acad Sci; 359:91-103 1981

The occurrence of the specific cellular retinol-binding protein previously identified in the fish-eye cytosol [CRBP(F)] was studied. [3H]-retinol binding assay showed the presence of CRBP(F) in 7/10 surgery specimens of hepatocellular carcinoma; CRBP(F) was detected in 4/5 patients with alpha-fetopr otein level of less than 200 nanog/ml. Vitamin A content in the tumor tissue was significantly lower than in the surrounding noncancerous tissue. The presence of CRBP(F) was also detected in the human fetal liver, in regenerating rat liver, and in hyperplastic liver nodules induced in rats by 2-acetylaminofluorene. CRBP(F) was found to be distinctly different from cellular retinoic acid-binding protein with respect to isoelectric point and relative electrophoretic mobility. These findings indicate that CRBP(F) can be considered as a novel onco-fetal protein, and that it is possible to prevent the experimental carcinogenesis by targeting retinoids to the hyperplastic nodules before hepatocellular carcinoma is established. (35 Refs)

FLUORENAMINES: IN VITRO

12. SPECIFIC LABELLING OF MICROSOMAL PROTEINS BY REACTIVE INTERMEDIATES GENERATED FROM 2-ACETYLAMINOFLUORENE IN VITRO.

Kaderbhai MA, Bradshaw TK, Freedman RB
Biological Lab., Univ. Kent, Canterbury, CT2 7NJ Kent, England
Chem Biol Interact; 36(2):211-227 1981

Incubetion of 2-[9-14C]acetylaminofluorene (2-[9-14C]AAF) in vitro with rat liver microsomes, leads to covalent binding of label to microsomal proteins. The binding is NADPH-dependent, increases linearly with time, and is inhibited by SKF-525A and 7,8-benzoflavone (7,8-BF). Binding is increased more than eight-fold in microsomes from 3-methylcholanthrene (MC)-pretreated rats, but only less than two-fold in those from phenobarbital (PB)-pretreated rats. In the presence of cytosolic proteins, there is slight enhancement of the labeling of microsomes and some labeling of the cytosolic proteins. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and two-dimensional gel electrophoresis indicate that covalent labeling by 2-AAF derivatives is concentrated in specific proteins. The pattern of labelling varies between microsomes from animals pretreated with PB, MC and 2-AAF. Factors which may contribute to the specificity of labeling are discussed. (Author abstract) (21 Refs)

13. CELL CYCLE REGULATION OF DNA REPAIR IN NORMAL AND REPAIR DEFICIENT HUMAN CELLS.

Gupta PK, Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, 3420 North Broad St., Philadelphia, PA, 19140
Chem Biol Interact; 36(1):19-31 1981

The regulation of nucleotide excision repair and base repair by normal and repair deficient human cells was determined. Synchronous cultures of WI-38 normal diploid fibroblasts and Xeroderma pigmentosum fibroblasts (complementation group D) (XP-D) were used to investigate whether DNA repair pathways were modulated during the cell cycle. Two criteria were used: (1) unscheduled DNA synthesis (UDS) in the presence of hydroxyurea (HU) after exposure to UV light or after exposure to N-acetoxy-acetylaminofluorene (N-AcO-AAF) to quantitate nucleotide excision repair or UDS after exposure to methylmethane sulfonate (MMS) to measure base excision repair; (2) repair replication into parental DNA in the absence of HU after exposure to UV light. Nucleotide excision repair after UV irradiation was induced in WI-38 fibroblasts during cell cycle reaching a max in cultures exposed 14-15 hr after cell stimulation. Similar results were observed after exposure to N-AcO-AAF. DNA repair was increased 2-4 fold after UV exposure and was increased 3-fold after N-AcO-AAF exposure. In either instance nucleotide excision repair was sequentially stimulated prior to the enhancement of base excision repair which was stimulated prior to the induction of DNA replication. In contrast XP-D failed to induce nucleotide excision repair after UV irradiation at any interval in the cell cycle. However, base excision repair and DNA replication were stimulated comparable to that enhancement observed in WI-38 cells. The distinctive induction of nucleotide excision repair and base excision repair prior to the onset of DNA replication suggests that separate DNA repair complexes may be formed during the eucaryotic cell cycle. (Author abstract) (31 Refs)

14. SPECIES DIFFERENCE IN LIVER MICROSOMAL AND CYTOSOLIC ENZYMES INVOLVED IN MUTAGENIC ACTIVATION OF N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Kaneda S, Seno T, Takeishi K
(c/o Takeishi) Dept. Immunology and Virology, Saitama Cancer Center Res. Inst., Ina-machi, Saitama-ken 362, Japan
JNCI; 67(3):549-555 1981

The mutagenic activations of N-hydroxy-N-2-fluorenylacetamide (N-OH-2-FAA) by subcellular fractions of the livers of rat, the mouse, guinea pig, hamster and monkey were examined for sensitivity to paraoxon, which inhibits a deacetylase but not an arylhydroxamic acid acyltransferase. The mutagenic activation by liver microsomes was almost entirely mediated by a paraoxon-sensitive enzyme in all the animals tested. In contrast the mutagenic activation by liver cytosol was mediated mostly by a paraoxon-sensitive enzyme in mice and guinea pigs, mostly by a paraoxon-resistant enzyme in rats and hamsters, and by both enzyme types in the monkey. In rats and guinea pigs, attempts were made to identify the enzymes causing mutagenic activation in the liver cytosol by a comparison of the elution positions of these enzymes in gel filtration and DEAE-cellulose column chromatography with those of known enzymes. In the rat liver cytosol, the mutagenic activation was mediated not only by acyltransferase but also by an unknown enzyme, which was resistant to paraoxon and differed from acyltransferase in chromatographic behavior. In the guinea pig liver cytosol, the activation was due to deacetylase activities, which could be separated into four fractions by gel filtration. These data indicate that species differ in the kinds of liver cytosolic enzymes involved in mutagenic activation of N-OH-2-FAA but not in the kind of liver microsomal enzyme involved. (Author abstract) (31 Refs)

15. THE EFFECT OF METABOLIC INHIBITORS ON THE LARGE PLAQUE EFFECT WITH HERPES SIMPLEX VIRUS.

Babich MA, Coohill TP, Snipes W, Taylor WD
(c/o Taylor) Biophysics Program, Pennsylvania State Univ., University Park, PA, 16802
Photochem Photobiol; 34(2):197-201 1981

Herpes simplex virus (HSV) macroplaque strain plaque development is faster on UV-irradiated African green monkey kidney cells if viral infection is delayed for 12 hr or more after cell irradiation. This phenomenon has been termed the large plaque effect (LPE). Here we show that treatment of UV-irradiated cells with cycloheximide inhibits the LPE. Pretreatment of unirradiated cells with hydroxyurea, caffeine, or acetoxyacetylaminofluorene results in faster plaque development. Treatment of UV-irradiated cells with either hydroxyurea or caffeine gave a LPE of the same magnitude as UV alone. In addition, the LPE was observed with other HSV strains - microplaque, syn-20, and KOS. Our results are consistent with the interpretation that the LPE is 'inducible' in African green monkey kidney cells and that inhibition of DNA synthesis is the inducing event. Possible causes of the LPE and similarities between the LPE and enhanced viral reactivation are discussed. (Author abstract) (25 Refs)

16. CHARACTERIZATION AND QUANTITATION OF A BALB/C HOST-MEDIATED ASSAY FOR MAMMALIAN CELL TRANSFORMATION BY CHEMICAL CARCINOGENS.

Barnett JW
The University of Texas Graduate School, Galveston, TX
Diss Abstr Int (B); 41(12):4483-B 1981

The peritoneal cavity of the BALB/c mouse was chosen as the depot for the syngeneic BALB/3T3 A31-1-D mammalian cell line to undergo host-mediated chemical exposure. Cells were recovered following four host incubation and the carcinogenic response to chemical agents was monitored by standard in vitro cell transformation bioassay using a focus formation endpoint. Companion in vitro cell transformation assays have also been evaluated by direct application of the same series of carcinogens. Additional experiments were performed to accurately quantify and monitor recovered cell populations to determine the effects of in vivo exposure. Four chemical carcinogens were tested by host-mediated and in vitro transformation assays, and a non-carcinogen, pyrene, tested by host-mediated assay. The direct acting agent ethyl methanesulfonate had positive transforming activity by both assay methods. Two chemicals which require metabolic activation, 2-aminofluorene and dimethylnitrosamine, demonstrated dose-dependent increases in transformation frequencies by host-mediated assay, and were non-transforming by in vitro test. Acrylonitrile, a suspect carcinogen, was positive for host-mediated transformation and negative in the in vitro assay. Py rene was non-transforming in the in vivo test system. (no Refs)

17. THE METABOLISM OF N-ACETYL-2-AMINOFLUORENE TO A MUTAGEN IN L5178Y/TK+/- MOUSE LYMPHOMA CELLS.

Amacher DE, Paillet SC, Elliot JA
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Mutat Res; 89(4):311-320 1981

The exposure of L5178Y TK+/- mouse lymphoma cells to N-acetyl-2-amino-fluorene (AAF) (4-9 x 10(-4) M) resulted in drug-induced cytotoxicity and slightly elevated mutant frequencies. The effect was shown to be dependent on the exposure time. The increase of mutant frequencies was negligible if the cells were treated with AAF for 3 hr. After an exposure time of 24 hr, however, a direct dose-dependent mutagenic response to AAF was observed. The increase of cytotoxicity was also shown to be dose-dependent in the 24 hr assay. The analysis of microsomal enzymes of disrupted L5178Y cell preparations revealed only a trace of N-demethylase activity (2.8 nanomole of formaldehyde was formed per mg protein/min). Benzo-(a)-pyrene hydroxylase was shown to be absent whereas AAF-N-hydroxylase activity was measurable. (30 Refs)

18. AN E COLI MICROSUSPENSION ASSAY FOR THE DETECTION OF DNA DAMAGE INDUCED BY DIRECT-ACTING AGENTS AND PROMUTAGENS.

McCarroll NE, Piper CE, Keech BH
Mutagenicity Section, Dept. Toxicology, Hazleton Lab. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180
Environ Mutagen; 3(4):429-444 1981

Seventy-seven compounds were examined for DNA-damaging activity in the Escherichia coli microsuspension assay (MSA). E coli strains WP2, WP2uvrA, CM611, WP67, WP100, W3110polA+, and p3478pola- were used. The noncarcinogen, 1-naphthylamine, which is weakly mutagenic in the Ames test and weakly genotoxic in the modified polA suspension assay, was negative in the MSA. No genotoxic activity was observed with 1-anthramine. It was suggested that the inactivity of the mutagenic carcinogens benzo(a)pyrene, 3-aminopyrene, and 4-nitrobiphenyl is related to the cell wall properties of E coli. Eight chemicals (mitomycin C, natulan, 5-bromo-2'-deoxyuridine, 5-fluoro-2'-deoxyuridine, thiacetarsamide, sodium arsenate, sodium arsenite, and sodium phenobarbital) which are not mutagenic in Salmonella were detected as DNA-modifying agents in the MSA. Six compounds (N-2-fluorenyl-acetamide, N-acetoxy-N-2-fluorenylacetamide, N-hydroxy-N-2-fluorenylacetamide, 2-nitrofluorene, 4-nitrobiphenyl, and benzo(a)pyrene) reported to be genetically active towards P3478 in a modified liquid suspension assay were negative in the MSA test with the DNA polymerase deficient strain. In this MSA, 77% of the 51 known or suspected carcinogens induced genetic damage in E coli and thus compared favorably with compilation appraisals of Salmonella assays. (35 Refs)

OTHER FUSED RING AMINES

19. CYTOLOGIC CHECKUPS FOR PERSONS OCCUPATIONALLY EXPOSED TO THE RISK OF URINARY TRA CT TUMORS (MEETING ABSTRACT).

Forni A
Clinica del Lavoro 'L. Devoto', Universita di Milano, Milan, Italy
Tumori; 67(2,SupplA):132 1981

Cytologic monitoring of the urinary sediment has been the method of choice for early diagnosis of urinary tract neoplasms in persons at risk for several decades, especially, therefore, in workers exposed to aromatic amines currently or in the past. Our personal experience in this matter involves the monitoring of approx 1750 dye factory workers with previous exposure to carcinogenic aromatic amines (benzidine, 1-naphthylamine , and 2-naphthylamine) and/or current exposure to other minor amines, possible carcinogenic, for a total of more than 20,000 urine samples. Cytology resulted in the initial diagnosis of 25 new cases of urinary tract tumors (including one case of kidney tumor) and 29 recurrences. Cystoscopic and/or histologic confirmation was obtained within 1 mo in some cases but only after mo or yr in others. Two new cases and 4 recurrences of grade 0 or 1 small papillary tumors and 1 case of kidney tumor were negative to cytologic monitoring. Among the cases diagnosed by cytology there were 2 cases of non-papillary carcinoma-in-situ confirmed by biopsy; it can nevertheless be asserted that at least a portion of the cases which were positive cytologically for a long time before cystoscopic confirmation represented phases of carcinoma-in-situ which could not be diagnosed by cystoscopy and were unconfirmed because of failure to perform a biopsy. During the monitoring period some of the workers occasionally had suspicious cytology reports with nonspecific cystoscopy reports of inflammation, hyperemia or bullous edema; the return to normal of the cytology reports in these cases suggests that moderate epithelial atypias can regress. Our own findings, in full accord with those of other groups, confirm the value of urinary cytology in the diagnosis of non-papillary carcinoma and high grade papillary carcinoma while substantiating its poor effectiveness in the diagnosis of low-grade forms lacking cellular atypia. (no Refs) (In ITA)

20. CO-MUTAGENIC EFFECTS OF 2-AMINOANTHRACENE AND CIGARETTE SMOKE CONDENSATE ON SMOKER'S URINE IN THE AMES SALMONELLA ASSAY SYSTEM.

Hannan MA, Recio L, Deluca PP, Enoch H
McDowell Cancer Network, Univ. Kentucky, Lexington, KY, 40536
Cancer Lett; 13(3):203-212 1981

Cigarette smoke condensate (CSC), benzo[a]pyrene, and aromatic amine 2-aminoanthracene (2-AA) were shown to be indirect mutagens in the TA98 strain of Salmonella typhimurium. The combination of CSC and 2-AA had a synergistic effect on histidine reversion. The enhancement of the mutagenic activity of 2-AA by CSC in TA98 salmonella was dose-dependent. The co-mutagenic effect of SCS was shown to be specific. No co-mutagenic effect was exhibited when CSC was in combination with either ethylmethane sulfon ate, methylmethane sulfonate, or 9,10-dimethyl-1,2-benzanthracene. In order to investigate the factor(s) in CSC that are responsible for the co-mutagenic activity in combination with 2-AA in a human body fluid, urine samples of cigarette smokers (2 packs/day) were tested in the Ames assay. Only the mutagenicity of 2-AA was enhanced by smoker's urine extract. Since the brand of cigarettes from which CSC was obtained was different from those smoked by the individuals who provided the urine samples, the results indicated that there is a co-mutagenic factor present in cigarette smoke. (20 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

21. SPECIAL COMBINATION OF ANTICANCER DRUG WITH ITS ANTIDOTE FOR CHEMOTHERAPY OF HEPATIC METASTASIS IN RAT.

Nishikawa K
Cancer Res. Institute, Kyushu Univ. Faculty Medicine, Fukuoka 812, Japan
Fuknoka Igaku Zasshi; 72(5):290-299 1981

Female Wistar King A rats bearing metastatic hepatoma or sarcoma of the liver were given infusions of nitrogen mustard N-oxide (NMNO; 10 or 20 mg/kg body wt) and its antidote, cysteine (C; 500 mg/kg), via portal vein or hepatic artery catheters, and the antitumor effects of the combination were compared with effects of administration of either or both of the substances in other ways to identical rats. The sarcomas were transplanted from syngeneic rats bearing tumors induced by methyl-nitrosocyanamide, and the hepatomas were transplanted from syngeneic rats bearing tumors induced by 3'-methyl-dimethylaminoazobenzene. The best antitumor effects were observed in the group of rats that were administered the NMNO first via the hepatic artery and the C via the femoral vein. Side effects caused by the NMNO were remarkably reduced by the co-administration of the C. Almost no anticancer effect was observed when the NMNO was administered via the portal vein, and the anticancer effect of the NMNO was weak when it was administered systemically. The max tolerated dose of the NMNO could be increased 2x with this combination compared to administration of the anticancer agent alone. (16 Refs) (In JPN)

22. EXISTENCE OF A PRACTICAL THRESHOLD DOSE FOR THE HEPATOCARCINOGEN 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE IN RAT LIVER.

Hino O, Kitagawa T
Dept. Pathology, Cancer Inst., Kami-Ikebukuro 1-37-1, Toxhima-ku, Tokyo 170, Japan
Gan; 72(4):637-638 1981

The possible existence of a threshold dose for the potent hepatocarcinogen 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB) was examined in male Donryu rats. The rats were divided into eight groups (Groups 1-8) and were fed a diet containing 0, 1, 5, 10, 20, 60, 100, and 300 ppm 3'-Me-DAB, respectively. There was a small number of enzyme-altered islands (EAI)/square cm/rat in the livers of control rats (Group 1) at 36 wk of age. Apparently high incidences of EAI were scored from the livers of animals from Groups 6-8 (60, 100, and 300 ppm). However, the incidence in Group 5 rats (20 ppm) suddenly dropped to a level less than one-seventh that of the control group. The incidences of EAI in Groups 2-4 were also below that of the control animals. An inverted dose-effect relation was clearly demonstrated. The difference in EAI incidence between control Group 1 and Group 5 (20 ppm) was statistically significant (p less than 0.01). These results suggested that there is a practical threshold for 3'-Me-DAB between 20 and 60 ppm. (6 Refs)

23. IMMUNOHISTOCHEMICAL STUDIES OF ALPHA-FETOPROTEIN- AND ALBUMIN-CONTAINING CELLS IN THE LIVER DURING ONTOGENESIS AND THE EARLY STAGE OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE (3'ME-DAB) HEPATOCARCINOGENESIS.

Sasaki M, Dempo K, Kaku T, Satoh M, Mori M

Second Dept. Pathology, Sapporo Medical Coll., Sapporo-shi, Hokkaido 060, Japan

Kanzo; 22(2):254-265 1981

Single and simultaneous occurrence of alpha-fetoprotein (AFP) and albumin (ALB) in the liver of rat fetuses, neonatal rats and rats fed a 3'methyl-4-dimethylaminoazobenzene (3'Me-DAB) diet was studied by the peroxidase-labeled antibody method. In the very early stage of hepatocarcinogenesis, when maturation from oval cells to transitional cells began to occur, only AFP was found in the scant cytoplasm of transitional cells. In a more advanced stage, when maturation from oval cells to transitional cells and small hepatocytes occurred frequently, simultaneous presence of AFP and ALB was observed in those cells. When small hepatocytes assumed the appearances of hepatocytes, only ALB was found in them. By day 12 of gestation, AFP and ALB were already present in all hepatocytes. This tendency continued during the entire fetal life. After birth, AFP-containing cells gradually disappeared from the periphery of the hepatic lobe toward the central area. Finally, all hepatocytes contained only ALB. The fluctuation of AFP and/or ALB-containing cells in the early stage of 3'Me-DAB hepatocarcinogenesis was very similar to that of ontogenesis of rat liver. That is, the former retraced the process of ontogenic differentiation of the liver. (46 Refs) (In JPN)

24. GLUCOSE-6-PHOSPHATE DEHYDROGENASE AND GAMMA-GLUTAMYLTRANSPEPTIDASE ACTIVITIES IN THE LIVER DURING CHEMICALLY INDUCED HEPATOCARCINOGENESIS IN RATS AND MICE.

Kojima S, Hama Y, Kubodera A

Dept. Radiopharmacy, Sch. Pharmaceutical Sciences, Teikyo Univ., Suarashi 1019-1, Sagamiko-machi, Takui-gun, Kanagawa, Japan

Toxicol Appl Pharmacol; 60(1):26-32 1981

Male Donryu rats were divided into three groups. One group was fed a diet containing 0.06% 3'methyl-4-(dimethylamino) azobenzene (3'-Me-DAB). The second group was given 60 ppm diethylnitrosamine (DEN) in drinking water. The third group was a control. Eight-wk-old random-bred ddY m ice were divided into three groups. The first was fed 0.05% o-aminoazotoluene (o-AT). The second received 0.06% 3'-Me-DAB. The third was a control. Glucose-6-phosphate dehydrogenase (G-6-PDH) and gamma-glutamyltranspeptidase (g-GTP)activities were measured over a period of wk. The hepatic levels of G-6-PDH and g-GTP increased after the start of 3-Me-DAB, DEN, or g-GTP administration, decreased once, and then showed sustained increase. Sodium phenobarbital also raised the level of G-6-PDH in rat livers. The data suggest that induction of increased G-6-PDH levels may be closely related to hepatic g-GTP activity in hepatocarcinogenesis in rats and mice. (31 Refs)

HETEROCYCLIC AMINES

25. MALIGNANT FIBROUS HISTIOCYTOMA OF THE BONE INDUCED BY LOCAL APPLICATION OF 4-HYDROXYAMINOQUINOLINE 1-OXIDE IN RATS.

Mii Y

Dept. Orthopedic Surgery, Nara Prefectural Medical Univ., Nara, Japan

Nara Igaku Zasshi; 32(2):116-135 1981

Experimental malignant fibrous histiocytomas (MFHs) of the bone were induced in male Fischer rats by means of a single injection of 4-hydroxyaminoquinoline 1-oxide (4HQ) in the periosteum or bone marrow of rats tibias. The 4HQ (1, 2, 4, or 8 mg) was delivered in 0.5 ml of a 40% dimethylsulfoxide (DMSO) soln, and control rats were given a single injection of 0.5 ml of 40% DMSO alone. Periosteal MFHs were induced in 3/13 rats injected in the periosteum with 2 mg of the 4HQ and in 9/13 given 4 mg; the tumors occurred from wk 18-27 after injection. Bone MFHs were induced in 1/15 rats injected in the bone marrow with 2 mg of the 4HQ in 11/18 with 4 mg, and in 12/14 with 8 mg; the tumors occurred from wk 18-29. Histologically, most of the MFHs were subclassified as fibrous type, and distant metastases to the lungs or lymph nodes were observed in some rats with fibrous type MFHs. Serial sacrifice of the rats showed proliferation of spindle and round cells around the necrotic injection site by hr 72 after injection, proliferation of these cells, formation of fibrous structures by wk 2, and appearance of multi-nucleated cells at wk 14. The results indicated that this rat model would be useful for further study of the formation of human MFH. (37 Refs) (In JPN)

26. DNA MODIFICATION IN RAT LUNGS FOLLOWING INTRATRACHEAL OR SUBCUTANEOUS ADMINISTRATION OF 4-NITROQUINOLINE-1-OXIDE, BENZO[A]PYRENE OR 2-AMINOANTHRACENE.

Harpaz R, Mitchell C

Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115

Chem Biol Interact; 36(2):129-140 1981

Benzo[a]pyrene (BP)-,2-aminoanthracene (2AA)- and 4-nitroquinoline-1-oxide (4NQO)-mediated DNA modification were investigated in rat lungs by using alkaline sucrose gradient sedimentation. The exposure-route, the physicochemical nature of the administered compound and the number of treatments were all important in determining the extent of DNA modification. 4NQO produced qualitatively similar modification whether instilled intratracheally (it) as a suspension or injected sc in a soluble form. BP and 2AA produced no DNA alteration when injected sc; they did, however, modify DNA sedimentation when instilled as a suspension, but not until 24 hr after treatment. Furthermore, BP caused no DNA modification at any sampling time when instilled in a lipid solvent. In contrast to the DNA modification observed at 24 hr after a single it treatment with a BP suspension, no such alteration was detected 12 or 24 hr after the last of five similar daily treatments. These results are discussed with respect to mechanisms of differential transport, clearance and metabolism of administered carcinogens. (Author abstract) (36 Refs)

27. PRESERVATION OF GASTRIC GLAND CHARACTER IN TRANSPLANTABLE GASTRIC ADENOCARCINOMA (SG2B) OF RATS.

Kokubo T, Takahashi M, Kurokawa Y, Miyahara M, Furihara C, Matsushima T

Dept. Pathology, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan

Gan; 72(4):583-589 1981

The morphological and biochemical characteristics of a transplantable tumor line of rat gastric carcinoma (SG2B), that developed in a Wistar strain rat after treatment with N-methyl-N'-nitro-N-nitrosoguanidine and then 4-nitroquinoline 1-oxide were examined at the 60th passage. The tumor was serially transplanted into newborn rats by sc and ip routes and has been passed through 60 transplant generations over a 4-yr period. The tumors appeared to be well-differentiated tubular adenocarcinomas throughout successive passages, and at each generation transplants were almost identical to the original gastric adenocarcinoma as judged by light and electron microscopic observation. Ultrastructurally, the neoplastic cells contained abundant free ribosomes and exhibited few mucin granules. The microvilli on the apical cell surface were short and irregularly spaced. Electrophoresis showed that pepsinogens (Pg) 3 and 4 were present but no Pg 1 was detectable at the 60th passage, as was the case in the tissue at the 2nd and 5th passages. The tumor tissue has thus retained the morphological and biochemical character of a pyloric gland type tumor for a long time (over 4 yr) during serial transplantation. (Author abstract) (14 Refs)

28. EVIDENCE FOR THE EXISTENCE OF A FAMILY OF BACTERIAL NITROREDUCTASES CAPABLE OF ACTIVATING NITRATED POLYCYCLICS TO MUTAGENS.

McCoy EC, Rosenkranz HS, Mermelstein R

Center for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106

Environ Mutagen; 3(4):421-427 1981

Mutants of Salmonella typhimurium strain TA98 capable of growth in the presence of 1,8-dinitropyrene were selected and cloned in the absence of the nitropyrene. Approx 30% of the clonal isolates exhibited the required properties and one of these, designated TA98/1,8-DNP6, was selected for further characterization and to serve as the prototype of bacteria presumably having lost the ability to reduce dinitropyrenes to their mutagenic forms. This strain was not mutagenized by 1,8-dinitropyrene, the chemical used for its selection. It appears that TA98/1,8-DNP6 is a nitroreductase-deficient derivative of TA98. This hypothesis was further supported by the observation that the mutagenicity of other dinitropyrenes was also diminished when TA98/1,8-DNP6 was used as the tester strain. However the extent of decrease differed among the various dinitropyrene isomers. The mutagenicity of the nitroacridine Entozon and of 4-nitroquinoline-1-oxide, chemicals not acted upon by the classical nitroreductase, was not reduced. (20 Refs)

29. HERPES VIRUS INACTIVATION BY CHEMICAL CARCINOGENS: DIFFERENTIAL INACTIVATION OF HERPES SIMPLEX VIRUSES BY 4-NITROQUINOLINE 1-OXIDE AND RELATED COMPOUNDS.

Speelman D, Li JL, Ramanujam VM, Legator MS, Albrecht T

(c/o Albrecht) Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550

Environ Mutagen; 3(4):467-476 1981

The effect of 4-nitroquinoline 1-oxide (NQO) on several strains of herpes simplex type 1 (HSV-1) and type 2 (HSV-2) was determined. The relationship between chemical structure and virus inactivation was examined. Relative rates of inactivation were first determined with HSV-1 (strain KOS) and HSV-2 (strain 333) over a range of NQO doses. Loss of virus infectivity occurred at a minimum dose of 25 ug/ml NQO and increased as the concentration approached 200 ug/ml. HSV-1 strain KOS appeared more sensitive to NQO inactivation than HSV-2 strain 333 at various doses and intervals. The differences in rates of inactivation of these strains of HSV-1 and HSV-2 suggested that HSV-1 strains, in general, might be more susceptible to NQO inactivation. The data obtained with HSV-1 strains KET, Patton, and 71-15 and HSV-2 strains 79-18, 198, and MS at NQO doses of 50 ug/ml were consistent with those observed for HSV-1 strain KOS and HSV-2 strain 333, although strain KOS proved to be the most sensitive of the HSV-1 strains tested while strain 333 was the least sensitive of the HSV-2 strains tested. The structural specificity of 4-nitroquinolines required for HSV-2 inactivation was examined with a related group of chemicals. Resultant varying reductions in HSV infectivity indicated the specificity required for virus inactivation. (35 Refs)

REVIEWS AND OTHER RELATED STUDIES

30. CERTAIN ASPECTS OF THE CHEMISTRY OF AROMATIC AMINES (MEETING ABSTRACT).

Dubini M
Montedison S.P.A., Milan, Italy
Tumori; 67(2,SupplA):129 1981

The carcinogenic effect of benzidine, 2-naphthylamine, and 4-aminodiphenyl is realized via complex metabolic systems and it has not been possible up till now to identify a relation between the chemical structure of aromatic amines and their activity. The substituents present on the aromatic system considerably modify the chemical and physico-chemical characteristics of the products so that it is not possible to consider the 'aromatic amines' as a family of products similar in biological behavior. In addition, the principal pathways of synthesis of benzidine, 2-naphthylamine, and 4-aminodiphenyl were reviewed along with the problems which must be confronted as a result of substitution. (no Refs) (In ITA)

31. PCBS, DYES TOP LIST OF PAPER INDUSTRY TOXIC CHEMICAL CONCERNS FOR THE 80'S.

Festa JL
American Paper Inst.
Pulp Pap; 55(7):156-158,162 1981

The important toxic and health issues currently facing the forest products industry are reviewed. A list of major federal legislative authorities under which toxic substances are now being regulated is provided. Issues presented include cost of the proposed polychlorinated biphenyl ban and recent federal regulatory action, the possible link between wood dust and nasal cancer, attention now being focused on dyes derived from benzidine and its congeners and on formaldehyde, and worker safety studies being conducted by the National Institute for Occupational Safety and Health. The major federal requirements for record keeping and reporting on hazardous substances are discussed. (no Refs)

32. ANTIBODIES TO CARCINOGENS-DNA ADDUCTS.

Poirier MC
Lab. Experimental Pathology, NCI, NIH, Bethesda, MD, 20205
JNCI; 67(3):515-519 1981

The preparation of rabbit antibodies to carcinogen-DNA adducts, the sensitivity and specificity of the antibodies, and their uses in studying carcinogen binding in rat tissues and cell cultures are reviewed. Among the areas currently under investigation by radioimmunoassay are the nature and extent of carcinogen binding to liver and kidney DNA in rats fed 2-acetylaminofluorene and the determination and manipulation of DNA adducts in cultured cells exposed to N-acetoxy-2-acetylaminofluorene. Solid-phase immunoassays may make it possible to measure adducts in a single cell, and direct visualization of adducts on DNA by electron microscopy may enable the localization of a carcinogen with respect to proximity of single-strand gaps, repair patches, or replication complexes. (11 Refs)

33. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

Since the oral mucosa is more resistant to the actions of chemical carcinogens than skin, early attempts to produce experimental malignant oral tumors were largely unsuccessful. The induction of squamous cell carcinomas in the thin lining mucosa of the hamster cheek pouch is discussed in detail, including the standardization the model, metastases, solvents, electron microscopy, histochemistry, cell kinetics, co-carcinogenesis, nutritional status, and hormones. Problems associated with this model of carcinogenesis include the debate about whether the tissue is truly intraoral, that the cheek pouch is a site of immunological privilege, and the tissue is technically difficult to handle. Models of intra-oral carcinogenesis in extra-pouch sites include those using hamsters, mice, rats, and primates. The resistance of the oral mucosa to chemical carcinogens is discussed. At this time, the most suitable models of oral carcinogenesis are the hamster cheek pouch and tongue models using 9,10-dimethyl-1,2-benzanthracene and the rat palate model using 4-nitroquinoline N-oxide. (136 Refs)

34. EPIDEMIOLOGY OF OCCUPATIONAL TUMORS OF THE URINARY TRACT (MEETING ABSTRACT).

Rubino GF, Piolatto G
Universita Torino, Via Zuretti 29, Turin, Italy
Tumori; 67(2,SupplA):131 1981

Italian and international observations concerning the incidence of urinary tract tumors in persons assigned to dye production have led us to conduct this analytical study aimed at identifying the carcinogenicity of specific amines and groups of amines. The causes of death of 906 workers in a local company for which they had detailed information on workers' activity in various departments were reviewed. 36 deaths due to urinary tract tumors were found as opposed to the 1.23 which would be expected on the basis of nationwide mortality. The excess was especially prominent among those assigned to benzidine and beta-naphthylamine production and to a lesser extent among those exposed by use or intermittent contact with them. In addition, an incidence approx 60x that expected was found among those assigned to the production of fuchsin and safranine T. Analysis of the processes involved in the chemical synthesis of these agents indicated that the agents responsible for the oncogenic action are probably o-toluidine and ditolylbase. The epidemiologic data in the literature on the human carcinogenicity of using the individual amines are reviewed. (no Refs) (In ITA)

35. CHEMICAL CHARACTERIZATION OF DIRECT-ACTING AIRBORNE MUTAGENS: THE FUNCTIONAL GROUP.

Talcott RE, Harger W
Div. Toxicology and Physiology, Dept. Entomology, Univ. California, Riverside, CA
Mutat Res; 91(6):433-436 1981

The chemical nature of the functional group involved in mutagenesis caused by airborne substances was investigated. Air particulates from Durham, North Carolina was sampled, extracted with acetone, and analyzed by a) chromatography for primary aromatic amines and b) bioassay with Salmonella typhimurium TA98 as the target organism. Following reduction with sodium borohydride-copper(II) acetylacetonate, the air extracts were again tested for amines and bioassayed. Chemical reduction of five extracts eliminated liver-independent (directly acting) mutagenic activity, and clearly produced amines in the two samples taken during cold weather. The loss of mutagenesis after reduction, and its retrieval in amine-rich extracts upon oxidation, suggest that a major portion of the total mutagenic activity in air pollution particles is contributed by nitro-substituted compounds detectable as their corresponding amines. The mutagenic burden may increase in the winter mo as the air becomes enriched with nitroaromatic substances. (11 Refs)

36. MNDO MOLECULAR ORBITAL STUDY OF NITRENIUM IONS DERIVED FROM CARCINOGENIC AROMATIC AMINES AND AMIDES.

Ford GP, Scribner JD
Pacific Res. Foundation, 1124 Columbia St., Seattle, WA, 98104
J Am Chem Soc; 103(15):4281-4291 1981

Semiempirical molecular orbital calculations at the MNDO level predict that the aryl- and N-acetyl-N-arylnitrenium ions exist as ground-state singlets resulting from the preferential stabilization of this state relative to the triplet (the ground state of NH2+ and the aliphatic nitrenium ions) by electron transfer from the phenyl substituent to the formally electron-deficient nitrogen atom. Simple nucleophiles add to these ions, leading to stable sigma adducts with relative exothermicities which correctly reproduce the nucleophilic order OH- greater than NH3 greater than Cl- greater than H2O only if the effects of ion hydration are specifically accounted for. The aryl- and N-acetyl-N-arylnitrenium ions are predicted to be stable to unimolecular rearrangement. (Author abstract) (70 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. THE GENETIC TOXICOLOGY OF ALDRIN AND DIELDRIN.
Ashwood-Smith MJ
Environmental Toxicology Res. Group, Dept. Biology, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
Mutat Res; 86(2):137-154 1981

RADIATION CARCINOGENESIS

2. EFFECTS OF LOW-LEVEL RADIATION ON BIOLOGIC SYSTEMS: A LITERATURE REVIEW.
Best TL, Hoditschek B
Eastern New Mexico Univ., Portales, NM
Effects of Low-Level Radiation on Biologic Systems: A Literature Review. Available from National Technical Information Service, Springfield, VA, as SAND-80-7143:, 246 pp., 1981.

3. PHOTOCARCINOGENESIS: AN OVERVIEW.
Furbes PD
Skin and Cancer Hosp., 3322 North Broad St., Philadelphia, PA, 19140
J Invest Dermatol; 77(1):139-143 1981

DIETARY FACTORS IN CARCINOGENESIS

4. EPIDEMIOLOGICAL CORRELATIONS BETWEEN DIET AND CANCER FREQUENCY.
Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Cancer Res; 41(9,part2):3685-3689 1981

5. ROLE OF DIETARY FIBER IN DIVERTICULAR DISEASE AND COLON CANCER.
Talbot JM
Life Sciences Res. Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 20014
Fed Proc; 40(9):2337-2342 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

6. PRIMARY HEPATIC CANCER IN ALCOHOLICS.
Tamburro CH, Lee HM
Liver Res. Center, Div. Digestive Diseases and Nutrition, Univ. Louisville Health Sciences Center, 511 South Floyd St., Louisville, KY, 40232
Clin Gastroenterol; 10(2):457-477 1981

7. PANCREATIC CANCER AND ALCOHOL.
Okuda K, Ohnishi K
Dept. Medicine, Chiba Univ. Sch. Medicine, 1-8-1 Inohana, Chiba City (280), Japan
Clin Gastroenterol; 10(2):479-484 1981

8. HELMINTHS IN THE INDUCTION OF CANCER. II. SCHISTOSOMA HAEMATOBIUM AND BLADDER CANCER.
Schwartz DA
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9. GENETICS OF WILMS'S TUMOR.
Matsunaga E
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

10. NEOPLASMS: COMPARATIVE PATHOLOGY OF GROWTH IN ANIMALS, PLANTS, AND MAN.
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11. PULMONARY CARCINOGENESIS: ARYL HYDROCARBON HYDROXYLASE.
McLemore TL, Martin RR
Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Treat Res; 1:1-34 1981

12. THE GENETIC TOXICITY OF HYDROXYLAMINES.
Marfey P, Robinson E
Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
Mutat Res; 86(2):155-191 1981

MODIFICATION OF CARCINOGENESIS

13. MODIFYING FACTORS OF CHEMICAL CARCINOGENESIS.
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14. ANTIPROLIFERATIVE EFFECTS OF RETINOIDS RELATED TO THE CELL CYCLE-SPECIFIC INHIBITION OF ORNITHINE DECARBOXYLASE.
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Dept. Pharmacology, Univ. Arizona Coll. Medicine, Tucson, AZ, 85724
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VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

15. PATHOGENESIS OF THYMIC LYMPHOMAS IN C57BL MICE.
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Pathol Res Pract; 171(2):268-278 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

16. CRITICAL ASSESSMENT OF THE VALUE OF IN VITRO CELL TRANSFORMATION FOR PREDICTING IN VIVO CARCINOGENICITY OF CHEMICALS.
Brookes P
(c/o Lohman, P. H.), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 86(2):233-242 1981

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17. MAMMALIAN GENETICS AND CANCER.
Russell ES
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Prog Clin Biol Res 45: 327 pp., 1981.

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CHEMICAL CARCINOGENESIS

Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/02

FEBRUARY, 1982

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ANILINES AND EXTENDED ANILINES

1. STUDY OF IMMUNE RESPONSE IN WORKERS EXPOSED TO DIRECT DYES.

Korosteleva TA, Belokhvostova AT, Movsesjan KS, Kuznrtsov SI
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR

Vopr Onkol; 27(7):47-51 1981

This study of textile workers exposed to direct dyes established a relationship between the duration and degree of exposure and the blood serum level of carcinogen-protein complexes (3-hydroxyanthranilic acid and benzidine) and immune response. (Author abstract) (11 Refs)

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2. CARCINOGENICITY OF BENZIDINE, N,N'-DIACETYLBENZIDINE, AND N-HYDROXY-N,N'-DIACETYLBENZIDINE FOR FEMALE CD RATS.

Morton KC, Wang CY, Garner CD, Shirai T
Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Carcinogenesis; 2(8):747-752 1981

Female CD rats were given twice-weekly ip injections for 4 wk, beginning at 30 days of age. Each of nine groups was given one of the following doses: 20 or 70 umol benzidine (BZ)/mg body wt/ injection; 7, 22, or 70 umol N,N'-diacetylbenzidine (DAB)/kg; or 7, 22, or 70 umol N-hydroxy-N,N'-diacetylbenzidine (HDAB)/kg. A toxicity test showed HDAB to be the most toxic of the three compounds, producing chemical peritonitis and death in all animals given the higher dosage. Additional groups were given 10 or 30 umol of one of the three compounds. Toxicity was low in all groups. BZ and HDAB showed about equal carcinogenicity. The higher dose of BZ produced mammary tumors, classified as fibroadenomas or adenocarcinomas, in 41% of the animals tested. The same dose produced Zymbal's gland tumors, classified as adenomas or carcinomas, in 24% of the animals tested. DAB and HDAB appeared to be as potent as BZ in inducing tumors. HDAB produced local reactions in the peritoneum, indicating that it may be an activated carcinogenic form of BZ. (33 Refs)

3. BIOLOGICAL EFFECT OF PLATINUM(II) COMPLEXES WITH TWO DIFFERENT NEUTRAL LIGANDS OF CIS-(PTNH3LCL2) TYPE.

Ivanov VB, Chel'tsov PA, Shchelokov RN
N. S. Kurnakov Inst. General and Inorganic Chemistry, Moscow, USSR
Izv Akad Nauk SSSR [Biol]; (4):551-557 1981

The structure-activity relationship of a series of antitumor platinum(II) compounds was studied in maize seedling roots. All complexes tested were significantly less active than cis-dichlorodiaminoplatinum (II). Only benzylamine-containing complex produced selective inhibition of mitotic activity. (12 Refs) (In RUS)

FLUORENAMINES: IN VIVO

4. EARLY EVENTS DURING LIVER CARCINOGENESIS INVOLVING TWO CARCINOGEN:PROTEIN COMPLEXES.

Blackburn GR, Andrews JP, Custer RP, Sorof S
(c/o Sorof), Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Cancer Res; 41(10):4039-4049 1981

This report describes the relationships between the levels of two principal carcinogen:protein complexes and histological alterations that occur during carcinogenesis in rat liver by three carcinogens. An intragastric tracer dose of N-[9-14C]-2-fluorenylacetamide interacts in normal rat liver to form the principal cytosolic 14C-carcinogen:protein complex (2S; M.W. 14,700). Continued ingestion of any of three hepatocarcinogens causes the marked loss of the 2S complex and the concurrent gain of a large-mol-wt carcinogen:protein complex (7.5S; M.W. approx 150,000) 48 hr following a dose of N-[9-14C]-2-fluorenylacetamide. The reciprocal changes in amounts of the two complexes have the following properties. The alterations occur early during hepatocarcinogenesis. In contrast to other reported early events, chemical carcinogen is directly involved. The two labeled fluorenyl proteins are the principal 14C-carcinogen:protein complexes in rat liver cytosol. Formation of the two complexes apparently involves activation of the carcinogen N-2-fluorenylacetamide. The reciprocal effects are brought on by the ingestion of any of the three hepatocarcinogens, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, and ethionine. The loss of the 2S complex was previously demonstrated to be associated with the loss of the 2S protein itself (14,700-daltons polypeptide) to which the carcinogen is bound. The rate of inversion in concentrations of the two complexes is apparently related to the susceptibility of the strain and sex of rat to the carcinogen; the greater the susceptibility the more rapid is the rate. The time of the max inversion coincides approx with the appearance of putative malignant lesions. Cessation of N-2-fluorenylacetamide ingestion results in the symmetrical reversal of the reciprocal changes in the levels of the two complexes. Liver regeneration following partial hepatectomy brings about a moderate inversion of the levels of the two complexes, suggestive of the possibility that the cell proliferation associated with hepatocarcinogenesis may be casually related to the effects. Consistent with this possibility, the 2S protein has a mol wt like those of known polypeptide growth regulators. The effects on the 2S and 7.5S carcinogen:protein complexes are carcinogen group specific, inasmuch as the ingestion of any of three other types of liver carcinogens, namely, diethylnitrosamine,aflatoxin B, and thioacetamide, does not induce the reciprocal changes in the levels of the two complexes. The existence of such carcinogen group specificity suggests that chemical classes of carcinogens may be grouped on the basis of their common actions and effects on their target macromolecules. The generalizations to be derived from a classification of carcinogen group specificities seem likely to advance understanding of underlying events in chemical oncogenesis. (33 Refs)

5. PARTIAL PERSISTENCY OF 2-AMINOFLUORENE AND N-ACETYL-2-AMINOFLUORENE IN RAT LIVER DNA.

Visser A, Westra JG
Div. Chemical Carcinogenesis, Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., 121, Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Carcinogenesis; 2(8):737-740 1981

Male R-Amsterdam (Wistar-related) and Sprague Dawley rats received 0.5 ml of a soln of [ring-3H]N-acetyl-2-aminofluorene (AAF: 1.87 mg/ml, ip). They were sacrificed at various times after injection of a single dose. The livers were homogenized. Hepatic DNA was isolated using RNAse and proteinase and precipitated as a salt by adding N-hexadecyl-N-trimethylammonium bromide (cetavlon). Binding of AAF and 2-aminofluorene (AF) to the carbon-8 of guanine in the DNA was measured. The results showed a rapid decrease in interaction products during the first 2 wk post-injection, followed by a much lower decrease in the second 2 wk. The ratio of bound AAF to bound AF did not remain constant during the course of the decrease. About 15% of the original amount of the two compounds remained persistently bound. Total binding of AAF and AF in Sprague Dawley rats was about 38% of the amount bound in R-Amsterdam rats. About 33% of the AF and 50% of the AAF bound in R-Amsterdam rats was bound in the Sprague Dawley rats. The difference apparently is due to differences in metabolism of AAF between the two strains. (17 Refs)

6. DETECTION OF MAMMALIAN CELL MUTAGENS IN URINE FROM CARCINOGEN-DOSED MICE.

Amacher DE, Turner GN, Ellis JH
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CT, 06340
Mutat Res; 90(1):79-90 1981

Urine was collected from male CD-1 mice dosed by oral gavage with either 300 mg/kg 2-aminofluorene (AF), 150 mg/kg cyclophosphamide (CY), or 200 mg/kg lucanthone (LU), and added directly to L5178Y TK+/- mouse lymphoma cultures (heterozygous at the thymidine kinase locus for the induction of trifluorothymidine-resistant (TFT-R) mutants). After 3 hr incubation, urine from the three different groups of rats produced significant, dose-dependent increases in frequency of TFT-R mutants. When the drugs were tested directly as mutagens in L5178Y TK+/- cells, LU and CY were positive both with and without metabolic activation, but AF required activation. Significant differences in the direct response of Salmonella typhimurium and L5178Y cells to these compounds indicate that the two cell types may not detect the same chemical entities as proximate mutagens. Urinary metabolites of AF, CY, and either the parental molecule or metabolites of LU can readily be detected as mutagens in a mammalian cell assay. (28 Refs)

7. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

Sato K, Hatayama I, Hoshino K, Imai F, Tsuchida S, Sato T, Nishimura K, Tatematsu M, Ito N
Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan
Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, and gamma-glutamyltransferase with consideration of histological classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the first carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose or term of DENA. These results indicate that deviations of some enzymes, such as pyruvate kinase and fructose-1,6-bisphosphatase, as well as histological differentiation of the primary hepatomas are more strongly influenced by the first carcinogen than by the second under our administration schedules and that the degree of enzyme deviation shown by hepatomas produced by a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors. (Author abstract) (33 Refs)

FLUORENAMINES: IN VITRO

8. IN VIVO AND IN VITRO ETHYLENE OXIDE EXPOSURE OF HUMAN LYMPHOCYTES ASSESSED BY CHEMICAL STIMULATION OF UNSCHEDULED DNA SYNTHESIS.

Pero RW, Widegren B, Hogstedt B, Mitelman F
Wallenberg Lab., Univ. Lund, Fack 7031, 220 07 Lund 7, Sweden
Mutat Res; 83(2):271-289 1981

Evidence of toxic exposure to ethylene oxide (EO) in factory workers producing disposable medical equipment was sought in 17 exposed women and 11 unexposed female controls from the same plant. EO exposure was 0.5-1.0 ppb for 40 hr/wk in 12 packers and 5-10 ppb for 8 hr/wk in 4 sterilizers and 1 lab technician, using the measurement of N-acetoxy-2-acetylaminofluorene (NA-AAF)-induced unscheduled DNA synthesis (UDS) in lymphocytes as the assay. The results for the controls in this study agreed with previous results for unexposed subjects: age and/or chromosome aberrations increased in a positive linear manner with increases in NA-AAF-induced UDS. However, the results for the EO-exposed packers were completely different for these two parameters: tendencies toward negative linear correlations were observed that were so divergent from controls (even for this small sample size) that these two groups were shown to be borderline significantly different populations. The data for the other group of exposed workers was nearly significantly different from that for the packers, indicating that perhaps the EO exposure in this group was not high enough to cause a significant reduction in NA-AAF-induced UDS. These results were corroborated by in vitro measurements of EO-induced (0.1-30 milliM) UDS in cultured lymphocytes: at greater than 2 milliM EO, UDS was inhibited, and even at the 0.1 milliM dose where UDS was not affected the exposed cells were sensitized to further exposure to NA-AAF, which caused a 40% cytotoxicity compared with 5% in controls. EO is toxic to lymphocytes and nontoxic doses of EO can sensitize cells to the cytotoxic action of other mutagens. (21 Refs)

9. NITRATED FLUORENE DERIVATIVES ARE POTENT FRAMESHIFT MUTAGENS.

McCoy EC, Rosenkranz EJ, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Sch. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 90(1):11-20 1981

The structure-activity relationship of polynitrated polycyclic aromatic hydrocarbons (PAH) which might be present in the environment as a result of incomplete combustion and subsequent nitration by oxides of nitrogen was investigated. The biological activity of 2-nitrofluorene, 2,7-dinitrofluorene, 2,7-diaminofluorene, (2,4,7-trinitro-9-fluorenylidene) malononitrile, 2,4,5,7-tetranitro-9-fluorenone, 2,7-dinitro-9-fluorenone, and 2,4,7-trinitro-9-fluorenone was studied. Significant mutagenic activity was observed for all the compounds in Salmonella typhimurium strains TA1538, TA98, and TA1537; a corresponding lack of activity or only minimal activity was observed in strain TA1535 and in Escherichia coli WP2 uvrA, indicating a frameshift type of mutagenicity. Mutagenic action is based on a reduction of the nitro-function to the corresponding hydroxylamines, the penultimate mutagens, which following esterification to electrophiles apparently react with the guanine moiety of DNA to form adducts. Max mutagenic activity was observed with the trinitro-substituted compound; addition of a fourth nitro group resulted in diminished activity, presumably reflect-ing steric hindrance of either enzyme reduction of the nitro-function or of DNA-adduct formation. (45 Refs)

10. INDUCTION OF 6-THIOGUANINE RESISTANCE IN SYNCHRONIZED HUMAN FIBROBLAST CELLS TREATED WITH METHYL METHANESULFONATE, N-ACETOXY-2-ACETYLAMINOFLUORENE AND N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Huang SL, Huang SM, Casperson C, Waters MD
Northrop Services, Inc., Research Triangle Park, NC, 27709
Mutat Res; 83(2):251-260 1981

The conditions required for inducing mutations in cultured, synchronized human fibroblasts were studied by examining induction of 6-thioguanine (6TG) resistance in these cells following treatment with methyl methanesulfonate (MMS; 6.25-25 ug/ml), N-acetoxy-2-acetylaminofluorene (NA-AAF; 7.5-17.5 uM), or N-methyl-N'nitro-N-nitrosoguanidine (MNNG; 5-80 uM) at different times during the G1, S, and G2 phases of the cell cycle. NA-AAF mutagenesis was dose-dependent when it occurred; NA-AAF induced no mutations during G1; but it induced an increasing frequency of mutations during S phase, with the highest frequency occurring simultaneously with the peak in DNA synthesis and the frequency declining thereafter. MMS induced mutations in treatment that included G1 and S phases and S and G2 phases, but not in the treatment that included G2 and G1 phases, indicating that mutagenesis requires DNA synthesis. Induction of mutation by MNNG followed one-hit kinetics, but mutations resulting from NA-AAF followed a higher-order function. All three chemicals resulted in an increase both in the mutation frequency and in the absolute number of mutants. Mutation in the cells studied appears to require the use of S-phase cells, regardless of the mutagenic agent used. (29 Refs)

11. COMPARISONS OF THE EFFECTS OF CHEMICAL CARCINOGENS IN MIXED CULTURES OF RAT HEPATOCYTES AND HUMAN FIBROBLASTS.

Strom S, Kligerman AD, Michalopoulos G
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
Carcinogenesis; 2(8):709-715 1981

Human male diploid fibroblasts (strain GM 3468) and parenchymal hepatocytes from male Sprague Dawley rats were treated separately and in mixed cell cultures with benzo[a]pyrene (BP), diethylnitrosamine (DEN), or 2-acetylaminofluorene (AAF). Fibroblast DNA was prelabeled with 5-bromo-2'-deoxyuridine. After exposure to the carcinogens, fibroblast and hepatocyte DNA was analyzed for unscheduled DNA synthesis (UDS). Fibroblast and hepatocyte DNA from mixed cultures was separated by isopycnic centrifugation in neutral cesium chloride. The hepatocarcinogens DEN and AAF produced increased UDS in hepatocytes, but not in fibroblasts, either separately or in mixed cultures. BP, a non-hepatocarcinogen, produced more UDS in in fibroblasts than in hepatocytes in mixed cultures. More BP was bound to fibroblast DNA than to hepatocyte DNA. BP bound to DNA from cultures of fibroblast alone was about 30% of that bound to fibroblast DNA from mixed cultures. BP produced no UDS in fibroblast in the absence of hepatocytes. Evidently the hepatocytes activated the UDS-promoting capacity of BP, which then was passed to the fibroblasts. The results obtained with BP, DEN, and AAF correspond to previous in vivo observations of the tissue-specific carcinogenicity of the three agents. The possibility that intercellular distribution may play a role in carcinogenic effects is indicated. (37 Refs)

OTHER FUSED RING AMINES

12. ALTERATIONS IN DRUG-METABOLIZING ENZYMES DURING FEEDING OF THE CARCINOGEN 2-AMINOANTHRAQUINONE.

Ramanathan R, Reddy TV, Weisburger EK
Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Toxicol Appl Pharmacol; 60(2):204-212 1981

Changes in enzymes which metabolize drugs during periods of feeding with 2-aminoanthraquinone (AAQ), at carcinogenic levels, were studied in young female Fischer 344 rats. Rats were fed 2% AAQ for 2, 4, 8 or 14 wk; after treatment, some were returned to the control diet. Some rats on the control diet were pair-fed with the AAQ group. At least four rats were available for each enzyme determination. Controls were fed ad libitum. Feeding AAQ increased liver content of cytochrome P-450, cytochrome b5, and increased NADPH-cytochrome c reductase activity as early as 2 wk. After 4 wk of AAQ, there was no change in azodye reductase, although an increase was observed in pair-fed controls. However, after 8 and 14 wk of AAQ, there was a significant increase in dimethylaminoazobenzene reductase. AAQ feeding also led to increased activities of benzo(a)pyrene hydroxylase, epoxide hydrolase, and alpha-naphthol-O-glucuronyl transferase. AAQ feeding beyond 4 wk increased the activities of N-demethylases, aniline hydroxylase and azo reductase. After the experimental period of AAQ feeding, the measured enzyme activities during the recovery period remained elevated in rats fed AAQ for 14 wk for 1 or 2 wk, and 2-4 wk in rats fed AAQ for 8 wk. (22 Refs)

13. CLASSIFICATION OF CHEMICAL AGENTS AS TO THEIR ABILITY TO INDUCE LONG- OR SHORT-PATCH DNA REPAIR IN HUMAN CELLS.

Francis AA, Snyder RD, Dunn WC, Regan JD
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 83(2):159-169 1981

The excision repair response of normal human fibroblasts (NHF) and of xeroderma pigmentosum (XP) cells to 33 chemicals was compared with that to UV irradiation (which is known to induce 'long-patch' repair of about 90 nucleotides) and to gamma irradiation (which is known to induce 'short-patch' repair of 3-4 nucleotides) by the 5-bromodeoxyuridine (BrdU) photolysis assay that quantitates unscheduled DNA synthesis. The following chemicals induced long-patch repair of 30-70 nucleotides in length and may be classified as UV-mimetic agents: N'-acetoxyacetylaminofluorene, ICR-170, 4-nitroquinoline-1-oxide, diarylcarbamate, 7-bromomethylbenzanthracene, dimethylbenzanthracene-5,6-epoxide, 7beta,8alpha-diol-9beta,10beta-epoxybenzo[a]pyrene, 7beta,8alpha-diol-9alpha,10alpha-epoxybenzo[a]pyrene, ethyl methanesulfonate, methyl methanesulfonate, and N-hydroxy-1-naphthylamine. The other chemicals elicited short-patch repair in NHF cells; the measurable DNA repair activity was at the limit of resolution of the sucrose density gradient technique employed to assay it. XP cells could not repair damage by these latter chemicals to the same extent that NHF cells could. It appears that, for the chemicals tested here, the ability of an agent to elicit a long-patch DNA repair response from NHF is a property of the most active direct-acting carcinogens. (23 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

14. THE EFFECT OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE ON FOETAL RAT HEPATOCYTES IN CULTURE.

Yeoh GC
Dept. Physiology, Univ. Western Australia, Nedlands, 6009, Western Australia
Eur J Cancer Clin Oncol; 17(7):743-752 1981

In hepatocyte cultures derived from 15-day and 19-day rat fetuses tyrosine aminotransferase accumulates during culture. In 15-day fetal hepatocytes enzyme is not detectable on day 1, whereas enzyme is already present in 19-day fetal hepatocytes at the same time. The effect of the hepatocarcinogen, 3'-methyl-4-dimethylaminoazobenzene (MDAB) on these two populations of differentiating hepatocytes is the subject of this study. This was undertaken to test the proposal that carcinogens may exert their effect on differentiating precursor cells. In cultures of 19-day fetal hepatocytes, accumulation of tyrosine aminotransferase is suppressed by MDAB whereas other liver enzyme markers examined, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, are not depressed. It is inferred from this result that hepatocytes that are about to initiate synthesis of tyrosine aminotransferase are prevented from doing so by the action of the carcinogen. In contrast, the synthesis of phosphoenolpyruvate carboxykinase by these cells which was initiated much earlier in development is unaffected. These findings would be consistent with the concept that carcinogens affect differentiating cells. In 15-day fetal hepatocytes, contrary to expectation, no effect of the hepatocarcinogen could be demonstrated. It is suggested that this may be due to the inability of the very immature hepatocytes to activate the hepatocarcinogen. In agreement with the biochemical data, the 19-day fetal hepatocytes but not the 15-day fetal hepatocytes display altered morphology when exposed to MDAB. (Author abstract) (17 Refs)

15. POLYAMINE CONCENTRATION, ACTIVITY OF THE RIBOSOMAL DISSOCIATION FACTOR AND PROPORTION OF RIBOSOMES ACTIVE IN PROTEIN SYNTHESIS IN THE 4-DIMETHYLAMINOAZOBENZENE-INDUCED RAT HEPATOMA.

Comolli R, Riboni L
Centro per lo Studio della Patologia cellulare del C.N.R., Universita di Milano, via Mangiagalli, 31, I-20133 Milano, Italy
Cancer Lett; 14(1):77-83 1981

The activity of the ribosomal dissociation factor in the high salt ribosomal wash and in the particle free cytoplasm of 4-dimethylaminoazobenzene (DAB)-induced liver tumors as compared to the livers of control rats was investigated and the proportion of ribosomes active in protein synthesis and the concentration of the polyamines spermine, spermidine and putrescine were determined. While the spontaneous dissociation of ribosomal preparations from DAB hepatoma was higher than from control liver, the addition of ribosomal wash extract and supernatant extract from the hepatoma caused a decrease in dissociation. The addition of control liver dissociation factor extracts to normal ribosomal preparations caused an increase in dissociation into active subunits. The proportion of ribosomes active in protein synthesis as indicated by sucrose density gradient analysis was significantly lower in tumor tissue. A significant decrease of putrescine in the DAB tumor cell extracts was noted, compared to normal rat liver. The spermidine/putrescine and (spermidine plus spermine)/putrescine ratios increased, predisposing towards association of the subunits. (22 Refs)

16. THE RELATIONSHIP BETWEEN TISSUE MORFHOLOGY IN EXPERIMENTAL LIVER CANCER AND SYSTEMIC ORGAN BLOOD FLOW: A STUDY BY SYSTEMIC AUTORADIOGRAPHY.

Matsuo K
First Dept. Internal Medicine, Sch. Medicine, Toho Univ., Ota-ku, Tokyo 143, Japan
Myakkangaku; 21(2):109-117 1981

The relationship between the histomorphological changes during the growth of experimental liver cancer induced by 3'-methyl-4-dimethylaminoazobenzen (3'-Me-DAB) and the changes in systemic organ blood flow determined by systemic autoradiography with 14C-dextran carboxyl was studied by determining the degree of blackening in vivo and unit tissue blood flow in vitro. The relation between the tissue profiles of hepatic tumors and their size was also studied. Morphological changes resulting from the development of experimental liver cancer were investigated in four stages. Namely, the lobule destruction stage (up to the 5th wk), the regeneration stage (from the 6th to the 7th wk), the redestruction stage (from the 8th to the 13th wk) and the tumor forming stage (in and after the 14th wk). Unlike human hepatocellular liver cancer, the tissues affected by hepatic tumors were classified into hepatocellular liver cancer, epithelial cellular cholangioma and mixed type carcinoma. With systemic autoradiography, only the kidney displayed excretion 60 sec later, other organs showing no changes. The blood flow in the livers of Donryu male rats determined for 23 wk after administration of 3'-Me-DAB showed a 5.25% decrease for the lobule destruction stage, a 21.54% increase for the regeneration stage, a 105.25% increase for the redestruction stage, a 13.51% decrease for the tumor forming stage and a 7.98% increase for the terminal stage. Autoradiography findings of the tumors could be classified into three groups. One showing remarkable increases in the degree of blackening, another showing a hive-shaped blackening arising from intra-tumoral increases and decreases in blackening and the rest showing a blackening of part of the surrounding area of the tumor accompanied by greatly reduced intra-tumoral blackening. In the in vitro study, the ratio of tissue blood flow between the tumoral and non-tumoral areas tumor region/surrounding region (T/S) ratio showed correlation with the size of the tumor. The av T/S ratio for hepatocellular liver cancer was 141.98%, that for mixed type carcinoma was 50.22% and that for epithelial cellular cholangioma was 25.02%. The T/S ratio decreased with the expansion of t he tumor, regardless of its tissue type. (20 Refs) (In JPN)

17. THE THYMIDINE INCORPORATION INHIBITING SCREENING SYSTEM (TTS) TO TEST CARCINOGENIC SUBSTANCES (A NUCLEAR DNA SYNTHESIS SUPPRESSIVE SHORT TERM TEST).

Amlacher E, Rudolph C
Inst. Pathology, Friedrich Schiller Univ., Ziegelmuhlenweg 1, 6900 Jena, E. Germany
Arch Geschwulstforsch; 51(7):605-610 1981

A short-term screening test is described in which the effects of carcinogens on DNA synthesis were measured by the determination of the mean number of silver grains per nucleus in the renal tubule and liver epithelia of 14-day-old CBA mice following ip injection of carcinogen. Fifteen hr after the injection of 0.1 ml of the dissolved chemical in a concentration representing 15/30% of the LD50, 3H-thymidine was injected ip. Autoradiographs of the nuclei of the renal tubular epithelia and of the liver epithelium were examined by visual silver grain counting. From this test, it was demonstrated that carcinogenic compounds of several different chemical classes (nitrosated amines, azo dyes, azo compounds, aliphatic iso- and heterocycles, aromatic amines, and metallic ions) partially inhibited the nuclear incorporation of thymidine in a significant manner over a time period longer than 24 hr. This decrease was expressed as a decrease of the mean of the silver grain number per nucleus in comparison with unaltered controls. This decrease was used as a criterion for the suppressive effect of carcinogenic substances on the rate of nuclear DNA synthesis. No false-positive results were obtained for noncarcinogenic compounds. The effectiveness of this test is discussed. (6 Refs)

18. EFFECTS OF HARMAN AND NORHARMAN ON THE METABOLISM OF ANILINE AND P-DIMETHYLAMINOAZOBENZENE.

Hayashi K
Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan
Nippon Eiseigaku Zasshi; 36(2):495-505 1981

The metabolism and mutagenicity of aniline and p-dimethylaminoazobenzene (p-DAB) were studied in vitro using rat liver microsomes. In the absence of harman (l-methyl-9H-pyrido[3,4-b]indole) and norharman (9H-pyrido[3,4-b]indole), p-DAB was metabolized to aniline without accumulation of p-methylaminoazobenzene (p-MAB) or p-aminoazobenzene (p-AAB). Aniline was metabolized to p-aminophenol (p-AP). Harman or norharman substantially inhibited metabolism of aniline to p-AP in microsomes. Norharman was a greater inhibitor than harman. Norharman slightly reduced the metabolism of p-DAB to aniline and caused the accumulation of p-DAB, p-MAB, and p-AAB. The metabolites of aniline, o-aminophenol, m-aminophenol, p-AP, and nitrosobenzene, were tested for mutagenicity in Salmonella typhimurium TA98. Nitrosobenzene was mutagenic only in the presence of norharman with S-9 mix. Similarly p-MAB, p-AAB, and aniline were mutagenic in TA98 only in the presence of norharman with S-9 mix. Harman and norharman each greatly inhibited aniline hydroxylase activity, while aminopyrene demethylase had only a slight effect. Aryl hydrocarbon hydroxylase was inhibited by norharman, but not by harman. (23 Refs) (In JPN)

HETEROCYCLIC AMINES

19. NITROSABLE DRUGS.

Ziebarth D
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 51(7):587-595 1981

The nitrosation of 61 potentially nitrosable drugs available for po administration in East Germany was studied in vitro under simulated conditions of the human stomach. Nitrosation of 10/61 drugs (aminophenazone, ampicillin, clomipramine, desipramine, ethambutol, imipramine, noramidopyrine methanesulfonate, oxacillin, phenoxymethylpenicillin, and piperazine) was observed. Nitrosodimethylamine, the principal product of aminophenazone, and mononitrosopiperazine, the principal product of piperazine, were identified chemically among the nitrosation products of the drugs. Both metabolites are carcinogenic for several animal species. The nitrosation of 9/10 drugs were inhibited 80-100% by ascorbic acid, and that of ampicillin by 18.2%. The findings indicate that po administered drugs forming carcinogenic N-nitroso compounds should be replaced by non-nitrosable drugs, and other potentially nitrosable drugs should be formulated with ascorbic acid, if they are compatible with this vitamin. (33 Refs) (In GER)

20. A POTENT MUTAGEN IN BROILED FISH. PART 1. 2-AMINO-3-METHYL-3H-IMIDAZO[4,5-F]QUINOLINE.

Kasai H, Yamaizumi Z, Nishimura S, Wakabayashi K, Nagao M, Sugimura T, Spingarn NE, Weisburger JH, Yokoyama S, Miyazawa T
Biology Div., Natl. Cancer Center Res. Inst., Chuo-ku, Tokyo, Japan
J Chem Soc [Perkin I]; (8):2290-2293 1981

Sun-dried sardines were broiled in normal fashion, ground, and extracted with methanol. The residue showed strong mutagenicity in Salmonella typhimurium strain TA98 in the presence of S-9 mixture, according to the Ames method. After further fractionation a neutral fraction was obtained that retained 40% of the mutagenicity of the original fraction. Purification yielded a mutagenic compound. The compound was identified by nuclear magnetic resonance spectrum and high- and low-resolution mass spectra as 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (AMIQ). The identification was confirmed by synthesis of the compound. The structure is a six-six-five-membered ring. The mutagenicity of AMIQ was much higher than that of other mutagens isolated from protein pyrolysis products. The cause of the high mutagenicity is as yet unknown. (32 Refs)

21. ALKALINE SUCROSE SEDIMENTATION ANALYSIS AS AN INDICATOR OF REPAIR CAPABILITY OF XERODERMA PIGMENTOSUM FIBROBLASTS FOR 4-NITROQUINOLINE-1-OXIDE DAMAGE.

Walker IG
Dept. Biochemistry, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Carcinogenesis; 2(8):691-695 1981

Fibroblasts were obtained from xeroderma pigmentosum (XP) strains in complementation groups designated A, B, C, E, and Variant, and from normal strains designated Ro, Gr, Fa, and Bu. Cells from all groups were exposed to 1 uM 4-nitroquinoline-1-oxide (4NQO) for 1 hr. They were either analyzed immediately or reincubated to allow repair of DNA damage. DNA sedimentation was measured in an alkaline sucrose gradient. In the brief lysis, gradients were allowed to stand in the dark for 30 min before centrifuging. In the long lysis, gradients were allowed to stand overnight before centrifuging. The long lysis technique showed repair of DNA in the normal strains and in the XP variant and group E strains. This repair was 50% complete 3 hr after removal of the 4NQO and fully complete after 6 hr. No repair was demonstrated in XP groups A, B, and C. The brief lysis technique showed DNA repair which was completed by 6 hr after removal of 4NQO. The repair was the same for all strains. The long lysis technique demonstrates a type of DNA damage not apparent under brief lysis. The results with the longer technique parallel results from other methods that indicate that cells from groups A, B, and C do not repair this type of damage. When alkaline sucrose gradients are used to measure DNA damage, the use of both the brief and long lysis methods is recommended. (26 Refs)

22. EFFECT OF INTERFERON ON REPAIR OF DAMAGED DNA.

Sinel'shchikova TA, Zasukhina GD
Inst. General Genetics, Moscow, USSR
Dokl Akad Nauk SSSR; 258(5):1231-1232 1981

The effect of interferon (IF) on the rate of repair of DNA breaks induced by 4-nitroquinoline-1-oxide was studied in cultured chick fibroblasts and in human lymphocytes. Coefficient of repair in IF-treated cells was 52%, compared with 41% in nontreated control cells. (4 Refs) (In RUS)

23. ELLIPTICINES AND HUMAN LIVER MICROSOMES: SPECTRAL INTERACTION WITH CYTOCHROME P-450 AND HYDROXYLATION. INHIBITION OF ARYL HYDROCARBON METABOLISM AND MUTAGENICITY.

Lesca P, Beaune P, Monsarrat B
Laboratoire de Pharmacologie, Toxicologie Fondamentales, 205 route de Narbonne, 31078 Toulouse Cedex, France
Chem Biol Interact; 36(3):299-309 1981

Some pharmacological properties of ellipticine (E) and its derivatives linked to their interaction with cytochrome P-450 have been investigated with human liver microsomes. 9-Hydroxyelipticine (9-OHE) interacts with human liver cytochrome P-450 exhibiting a Type II spectrum (lambdamax:428 nm, Ks = 1.1 uM). After incubation with human liver microsomes the E was converted to 9-OHE; 7-hydroxyellipticine was not produced. The cytotoxic effect of this biotransformation has been evaluated on leukemic L1 210 cells, in vitro, and found to be equal to those elicited by liver microsomes of control or phenobarbital (PB) pretreated rats. Moreover, 9-OHE and 9-fluoroellipticine (9-FE) strongly inhibit the benzo[a]pyrene hydroxylase (AHH) activity of human liver microsomes (I50 = 2.6 uM and 1.6 uM, respectively) as well as the mutagenesis induced by the polycyclic aromatic hydrocarbon 2-acetylaminofluorene (AAF); 1 ug/plate of each of these compounds is able to inhibit by more than 50% the mutagenicity of 5 ug/plate AAF. (Author abstract) (29 Refs)

REVIEWS AND OTHER RELATED STUDIES

24. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.

Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

Epidemiological studies of the carcinogenicity of hair dyes are complicated by (1) too broad a definition of occupation, with hazards to specific job categories being overlooked, and too narrow a definition, making the surveyed group too small to yield significant results, (2) exposure to competing or cooperating carcinogens, (3) uncertain influence of life style, (4) latency period and changes in occupation, and (5) changes and regional variations in occupational classification. A review of reports on cancer incidence among barbers, hairdressers, and their customers is made with respect to urinary bladder, lung, larynx, and breast. The evidence is still apparently insufficient to support a link between exposure to hair dye and cancer. Further research with more statistically valid sampling is recommended. (30 Refs)

25. A CASE-CONTROL STUDY OF BLADDER CANCER IN THE UNITED STATES RUBBER AND TYRE INDUSTRY.

Checkowway H, Smith AH, McMichael AJ, Jones FS, Monson RR, Tyroler HA

Occupational Health Studies Group, Sch. Public Health, Univ. North Carolina, Chapel Hill, NC, 27514

Br J Ind Med; 38(3):240-246 1981

A case-control study of bladder cancer was conducted in five United States rubber and tire companies to determine if there were high-risk jobs and work areas within the industry. The study included 220 male cases of bladder cancer, of whom 107 were identified from hospital record reviews and 113 from death certificates. Each case was matched individually with two industry controls by sex, race, yr of birth, and company. One control was matched additionally by yr of hire and duration of employment. Comparisons of cases and controls not matched by yr of hire and age of hire showed no differences for those variables, which suggests that age and calendar period of first exposure to the industry were not risk determinants. When the work histories of both cases and controls were contrasted it was found that cases were more likely than controls to have worked in milling (odds ratio (OR) = 1.91) and calender operation (OR = 2.21) jobs. The relative risk estimates for milling and calender operation both exhibited linear trends of increase with duration of exposure. Milling and calender operation jobs entail potential exposures to volatilized reaction products from heated rubber stock. A better understanding of etiological associations with job type will require more detailed characterization of the work environment with regard to the sources and levels of aromatic amines and other suspected bladder carcinogens. (Author abstract) (25 Refs)

26. EARLY DETECTION OF OCCUPATIONAL HAZARDS.

McDonald JC, Harrington JM

TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, London WC1E 7HT, England

J Soc Occup Med; 31(3):93-98 1981

Because of the rate of technological change, the time interval between exposure to a hazard and the appearance of its effects may be very long. Surveillance procedures for occupationally related diseases and injuries in Britain are generally regarded as inadequate. Reported intervals between the first suspicion and general acceptance of some occupational hazards have varied from 2 to 59 yr (for angiosarcoma due to vinyl chloride monomer and bladder cancer due to aromatic amines, respectively). Some occupational diseases have only been recognized by chance, having been completely missed by existing methods of reporting or the discovery was not reported. Detection of occupational hazards has frequently depended upon astute clinical observation; a system of rapid informal communication about such 'hunches' is needed. There are parallels for this idea in the history of determining the etiology of numerous communicable diseases. The essentially informal reporting networks for communicable diseases operating in Britain and the United States are linked to central analysis units which can initiate rapid field studies when indicated. The establishment of an analogous system for occupational disease is advocated. (no Refs)

27. SOME RISK FACTORS OF BREAST CANCER.

Scolozzi R, Salmi R, Coccafegli A, Dell'Acqua G
Istituto di Clinical Medica Generale e Terapia Medica, Universita, Ferrara, Italy

Recenti Prog Med; 70(5):463-486 1981

Studies on the risk factors of breast cancer are reviewed. High stature, overweight (obesity), early menarche, hyperestrogenic, reduced fertility, advanced age at first childbirth, short overall duration of lactation, high-caloric, high-fat diet, long-term use of oral contraceptives, especially before the first pregnancy, late menopause, and exposure to ionizing radiation, especially during and shortly after puberty are generally recognized risk factors along with family history of breast cancer. The long-term use of hair dyes, especially of permanent ones, is also considered a risk factor for breast cancer along with other cancers. (134 Refs) (In ITA)

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CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?

Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.

Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
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7. RADIOACTIVITY IN DRINKING WATER.

Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.

Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
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10. PANCREATIC CANCER.

Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.

Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.

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Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).

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Zh Eksp Klin Med; 21(3):287-292 1981
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15. LIFESTYLE AND CANCER.

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International Agency for Res. on Cancer, Lyon, France
Cancer Forum; 5(1):4-14 1981

16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.

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Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
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17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.

Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview) Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

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21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.

Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
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23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

24. BURKITT'S LYMPHOMA.

Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

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26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

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Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.

Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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CHEMICAL CARCINOGENESIS

Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/03

MARCH, 1982

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ANILINES AND EXTENDED ANILINES

1. PROSTAGLANDIN SYNTHETASE CATALYZED DNA STRAND BREAKS BY AROMATIC AMINES (MEETING ABSTRACT).

Rahimtula A, Moldeus P, Nordenskjoeld M, Andersson B
Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Several aromatic amines are renal medullary toxins and bladder carcinogens. We have found that the aromatic amines 2-naphthylamine, 2-4-diaminotoluene, p-aminophenol and p-phenetidine at a concentration of 50uM cause a 2-3 fold increase in DNA strand breaks in cultured human fibroblasts in the presence of sheep vesicular gland microsomes and arachidonic acid. Indomethacin and butylated hydroxyanisole inhibited this

HE 20. 3173/2:

reaction. Curiously, benzidine did not give rise to a significant increase in DNA strand breaks. Metabolism of these amines by prostaglandin synthetase was judged by their ability to complete with and inhibit another prostaglandin synthetase dependent reaction - the activation of paracetamol. An 0.1 mM concentration of these amines inhibited the glutathione conjugate formation of paracetamol by 60-90%. Covalent protein binding of [3H]paracetamol was similarly inhibited. At the concentration used these amines did not significantly affect the cyclooxygenase activity as judged by prostaglandin E2 and prostaglandin F2alpha formation. (2 Refs)

2. FEEDBACK CONTROL OF CHOLESTEROL BIOSYNTHESIS IN RATS FED THE LIVER CARCINOGENS BENZIDINE AND 2-ACETYLAMINOFLUORENE.

Depass LR, Morris MD
Bushy Run Res. Center, R.D. 4, Mellon Road, Export, PA, 15632
Cancer Biochem Biophys; 5(2):91-95 1981

Dietary feedback control (DFC) of hepatic cholesterol synthesis is absent in hepatomas of trout, mouse, rat and man. DFC has also been shown to be defective in rats fed several liver carcinogens, including 2-acetylaminofluorene (AAF). These studies have led to the hypothesis that loss of normal DFC is an early and necessary event in the development of liver cancer. To test this hypothesis, we fed the liver carcinogens benzidine (0.006% in drinking water) or AAF (0.05% in chow) to male Sprague-Dawley rats for either 3 or 6 wk. We measured cholesterol synthesis as the incorporation of 2-14C-acetate into digitonin-precipitable sterols by liver slices. DFC was tested by adding 2% cholesterol to the diet for 3 days prior to sacrifice. DFC was defective in the AAF-fed rats but was normal in the benzidine-treated rats. These results are at variance with the previously stated hypothesis and, for the first time, suggest that defective DFC is not a consistent finding in the early stages of liver carcinogenesis. Additional research is necessary to explain why DFC is altered by exposure to some liver carcinogens such as AAF but unaffected by exposure to others such as benzidine. (Author abstract) (20 Refs)

FLUORENAMINES: IN VIVO

3. DNA METHYLATION AND METHYLASE LEVELS IN NORMAL AND MALIGNANT MOUSE HEPATIC TISSUES.

Lapeyre JN, Walker MS, Becker FF
Dept. Pathology, Section Experimental Pathology, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Carcinogenesis; 2(9):873-878 1981

DNA methylation levels (expressed as the percentage of 5-methylcytosine relative to total cytosines) were measured in normal mouse liver, primary hepatocellular carcinomas (PHCs) in male C3H mice, PHCs induced in male C7Bl/6N mice by chlordane, N-acetylaminofluorene, or 3'methyl-4-dimethylami noazobenzene, and spontaneous and chemically induced PHCs in male (C7BL/6H x C3H/HeN)F1 (B6C3) mice. All tumors demonstrated an undermethylation of their genomes, compared with normal livers of age-matched controls. The undermethylation was not due to inactivation of or deficiency in DNA methylase activity, since enzyme levels in tumor nuclei were higher than background levels. The possibility that aberrations in DNA methylation are involved in the transformation of normal differentiated cells to neoplastic cells is discussed. (57 Refs)

4. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYLACETAMIDE-INDUCED RAT LIVER LESIONS.

Mori H, Tanaka T, Nishikawa A, Takahashi M, Williams GM
Dept. Pathology, Gifu Univ. Sch. of Medicine, 40 Tsukasa-machi, Gifu 500, Japan
Gan; 72(5):798-801 1981

The enhancing effects of phenobarbital (PB) and barbital on hepatotumorigenesis were compared by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats, 2 mo old, were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. The remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% barbital diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin stained or iron stained specimens per cm2 of the liver space at 16 wk in Group I was much lower than that at termination of FAA feeding. However, the numbers of Groups II and III were well maintained at 8 and 16 wk and those at 16 wk in both groups were significantly higher than that in Group I (p less than 0.001). These data show that barbital could be an enhancer of hepatotumorigenesis like PB. (Author abstract) (25 Refs)

5. RELATIONSHIP OF METABOLIC ACTIVATION OF N-HYDROXY-N-ACYLARYLAMINES TO BIOLOGICAL RESPONSE IN THE LIVER AND MAMMARY GLAND OF THE FEMALE CD RAT.

Shirai T, Fysh JM, Lee M, Vaught JB, King CM
(c/o King) Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(11,part1):4346-4353 1981

Ip injection of the N-formyl, N-acetyl, or N-propionyl derivatives of N-hydroxy-4-aminobiphenyl, N-hydroxy-2-acetylaminofluorene, or N-(4-biphenyl)glycolamide disclosed that the ability of these compounds to induce mammary tumors in the female CD rat was greater if the compound was able to be metabolized to a reactive product by one of two soluble enzymes obtained from both the liver and mammary gland. A similar but weaker association between the formation of gamma-glutamyltranspeptidase-positive foci and cellular altered foci of the liver was also observed. The enzyme related to the tumorigenicity of these compounds was characterized by a highly specific capacity to form adducts from the acetyl and propionyl derivatives. The other enzyme exhibited greater activity with N-formyl substrates. The two enzyme activities were separable by ion-exchange chromatography on DEAE-cellulose and by gel filtration of Sephacryl. Liver microsomes also possessed the capacity to activate both the formyl and acetyl derivatives to reactive species; formyl substrates were 7 to 8x more active than acetylated compounds. The microsomal activities and the formyl-preferring soluble enzyme were inhibited by diethyl-p-nitrophenylphosphate, a microsomal deacylase inhibitor. The cytosolic enzymes that are most active with the acetyl and propionyl substrates were little affected by this organophosphate compound. The microsomal activation was not due solely to deacylation of the hydroxamic acids, since formylated and acetylated substrates were hydrolyzed at approx the same rates. (Author abstract) (37 Refs)

6. EPOXIDE HYDROLASE AND HEPATOCARCINOGENESIS.

Griffin MJ
Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Trends Pharmacol Sci; 2(10):257-258 1981

The role of epoxide hydrolase (EH) in hepatocarcinogenesis is described. A search for markers associated with multistage development of preneoplastic cells through focal and nodular stages to a hepatoma led to the discovery of the preneoplastic (PN) antigen, a microsomal antigen present in nodule and hepatoma cells. Through immunological studies EH was found to be a major PN antigen. A class of heterocyclics, including isoquinoline, norharman, and ellipticine, has been shown to stimulate microsomal EH. The requirement for a pyridinic nitrogen beta to a ring fusion suggests enzyme dictated specificity, while the pyridinic nitrogen suggests an electrophilic target. Reactive electrophiles, such as epoxides, have been found to regulate cell function and development. Perhaps endogenously formed epoxides play a role in liver adaptation during hepatocarcinogenesis. All hepatocarcinogen tests seem to cause an early (1-5 wk) induction of EH activity and microsomal content of the enzyme protein. One explanation for this early induction of EH is the production of increased amounts of an endogenous epoxide as an acute response. EH regulation during hepatocarcinogenesis is discussed with 2-acetylaminofluorene hepatocarcinogenesis as an example. (12 Refs)

7. DOSE-DEPENDENCY OF 2-ACETYLAMINOFLUORENE BINDING TO LIVER DNA AND HEMOGLOBIN IN MICE AND RATS.

Pereira MA, Lin LH, Chang LW
Health Effects Res. Lab., US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicol Appl Pharmacol; 60(3):472-478 1981

Binding of 2-acetylaminofluorene (2-AAF) to liver DNA and Hb in Sprague-Dawley rats and CD-1 mice of both sexes was determined to test proposals that Hb binding correlates with target or gan DNA binding and carcinogenicity. In both species, 2-AAF binding to liver DNA and HB increased as a linear function of dose (1-100 umoles/kg, po). This indicated that the formation of reactive 2-AAF liver metabolites also was linearly related to dose. No sex difference was observed in 2-AAF macromolecular binding, except for an apparent higher liver DNA binding in female mice than in male mice. DNA binding was only 7x greater and Hb binding only 2.5x greater in rats than mice; thus the binding did not reflect the 246x greater carcinogenicity of 2-AAF in rat liver. The results indicated that Hb binding can be used to predict DNA binding and the systemic dose; however, the extent of DNA binding does not predict carcinogenic potency. (20 Refs)

FLUORENAMINES: IN VITRO

8. MOLECULAR STRUCTURES OF THREE HYDROXYL DERIVATIVES OF THE HEPATIC CARCINOGEN ACETYLAMINOFLUORENE. EVIDENCE FOR A PREFERRED ORIENTATION OF THE ACETYLAMINO SIDE-CHAIN.

Neidle S, Subbiah A, Mason A, Islam SA
Cancer Res. Campaign Biomolecular Structure Res. Group, Dept. Biophysics, Univ. London King's College, 26-29 Drury Lane, London WC2B 5RL, England
Carcinogenesis; 2(9):901-907 1981

The geometric parameters of three acetylaminofluorene (AFF) derivatives (1-hydroxyl-AAF, N-hydroxyl-AAF, and 3-hydroxyl-AAF) were compared. The results of x-ray crystallographic analysis indicated that all three derivatives have similar bond length and angle geometry. The marked differences in mutagenicity and carcinogenicity are explained by coplanar conformations of the side-chain. (27 Refs)

9. THE CARCINOGEN N-ACETOXY-ACETYLAMINOFLUORENE REACTS PREFERENTIALLY WITH A CONTROL REGION OF THE INTRACELLULAR SIMIAN VIRUS 40 CHROMOSOME (MEETING ABSTRACT).

Beard P, Kaneko M, Cerutti P
No affiliation given
Experientia; 37(6):638 1981

We have investigated the binding of the ultimate carcinogen N-acetoxy-acetylaminofluorene (AAAF) to specific regions of the SV40 chromosome in situ in the intact infected cell. SV40-infected cells late in the lytic cycle were incubated with 3H-AAAF. SV40 DNA was extracted, digested with restriction enzymes Hae III and Kpn I and radioactivity in each DNA fragment determined. The results indicated that a stretch of DNA near the origin of replication of the intracellular SV40 chromosome was more susceptible to attack by AAAF than the rest of the SV40 genome. When naked DNA was labeled with 3H-AAAF in vitro no hyperreactive region was seen. The hyperreactive region may represent a stretch of DNA which is nucleosome-free or has another unusual chromosomal structure. (no Refs)

10. ENZYMATIC METHYLATION OF MICROSOMAL METABOLITES OF BENZO(A)PYRENE.

Lombardi PE, Mayhew JW, Goldin BR, Gregory ME, Lynch MA, Sullivan CE, Gorbach SL
(c/o Mayhew) Infectious Disease Service, New England Medical Center Hosp., 171 H arrison Ave., Boston, MA, 02111
Cancer Res; 41(11,part1):4415-4419 1981

These studies suggest that the microsomal metabolism of benzo(a)pyrene (BP) produces metabolites which can be methylated by the catechol-o-methyltransferase (COMT)/S-adenosylmethionine (SAM) enzyme/donor combination. Induced microsomes converted 12 to 15% of substrate BP to polar products. Approx 0.06% of substrate BP was recovered as COMT/SAM-reactive substances. In tests for specificity, COMT/SAM was found to react with catechols, but not with dihydrodiols, quinones, a phenol, an epoxide, or 1,4-hydroquinone. Organic extracts of COMT/[14C]SAM incubations with BP were fractionated by high-performance liquid chromatography. The appearance of radiolabeled chromatographic bands required the presence of substrate BP, microsomes, and COMT/[14C]SAM.

When the Ames mutagenesis assay was supplemented with COMT/SAM, a 36% reduction was observed in the number of revertant colonies induced by the microsomal oxidation of BP. In contrast, the mutagenic properties of 2-aminofluorene were not affected by COMT/SAM. These observations indicate that COMT/SAM does not generally inhibit mixed-function oxidase activity but rather reacts with substances which are activated by ring oxygenations. (Author abstract) (33 Refs)

11. ENHANCEMENT OF N-HYDROXY-2-AMINOFLUORENE BACTERIAL MUTAGENICITY BY THE SOLUBLE PROTEIN FRACTION FROM RAT LIVER AND PARTIAL PURIFICATION OF THE ENHANCEMENT ACTIVITY.

Saccone GT, DasGupta BR, Pariza MW
(c/o Pariza) Dept. Food Microbiology and Toxicology, Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 41(11,part1):4600-4605 1981

Bacterial mutagenesis from 2-aminofluorene mediated by washed rat liver microsomes was elevated 2-to 3-fold by addition of the hepatic soluble protein fraction. Enhancement was observed at 2-aminofluorene concentrations between 1 and 20 ug/assay but not at 30 to 50 ug/assay. The soluble protein fraction (without added microsomes) did not activate 2-aminofluorene for bacterial mutagenesis. However, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was enhanced by the soluble protein fraction, but only when reduced nicotinamide adenine dinucleotide phosphate was also present On the basis of chemical assay, reduced nicotinamide adenine dinucleotide phosphate reduced 2-nitrosofluorene to N-hydroxy-2-aminofluorene and protected the hydroxylamine from oxidation, thus indicating that it was the mutagenicity of N-hydroxy-2-aminofluorene (but not 2-nitrosofluorene) which was enhanced by the soluble protein fraction. Without the added soluble protein fraction, mutagenesis by N-hydroxy-2-aminofluorene or 2-nitrosofluorene was unaffected by reduced nicotinamide adenine dinucleotide phosphate. We succeeded in partially purifying a protein fraction with properties of the enhancement activity. The partially puri fied fraction, which represents a 14-fold increase in specific activity, was assigned a mol wt of 33,500 by gel filtration through Sephadex G-100. This fraction was resolved into three components by polyacrylamide gel electrophoresis; the mol wt of the three components were determined by sodium dodecyl sulfate-polyacrylamide gel (10%) electrophoresis to be 33,000, 27,000, and 16,250. The mechanism of mutagenesis enhancement remains unknown. (Author abstract) (27 Refs)

12. ACTIVATION OF N-2-ACETYLAMINOFLUORENE BY TARGET AND NONTARGET SYRIAN GOLDEN HAMSTER CELLS (MEETING ABSTRACT).

Poiley JA, Raineri R, Ernst MK, Andrews AW, Pienta RJ
Frederick Cancer Research Center, Frederick, MD, 21701
In Vitro; 17(3):222 1981

The ability to metabolize and activate N-2 acetylaminofluorene (AAF) of Syrian golden hamster kidney, bladder, small intestine, lung and liver cells was compared with that of hamster embryo fibroblasts. At varying times after isolation, cells were exposed to 5 ug [14C]-AAF for 3, 6 or 24 hr. The level of AAF remaining and the amount bound to cellular components were determined. Within 3 hr, hepatocytes and intestinal cells had metabolized 95% of the AAF. Within 6 hr lung cells had metabolized 50%, and kidney cells 20%. By contrast, fibroblasts and bladder cells had metabolized only 20-25% in 24 hr. The amount of material bound to cellular components was proportional to the amount of AAF metabolized. A second measure of activation was the ability of intact organ cells to metabolize AAF to a form mutagenic in Salmonella TA 1538. Revertant numbers were much increased above background with hepatocytes (240-fold), lung cells (11-fold), intestinal cells (5-fold) and kidney cells (2-fold). With bladder cells and fibroblasts, revertant numbers were not significantly higher. We have demonstrated that intact cells, whether or not from the target organ, can metabolize AAF at a high rate to forms which either bind to cellular components or are excreted. These forms are also mutagenic in Salmonella. (no Refs)

13. PEROXIDASE ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS (MEETING ABSTRACT).

Wong PK, Hampton MJ, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Rat mammary gland parenchymal cells activate N-hydroxy-2-acetylaminofluorene (N-OH-AAF) to 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAC-AAF) via a nitroxyl free radical form of the carcinogen. Prostaglandin synthetase has a peroxidase activity and hence we have examined parenchymal cells to determine if the activation of N-OH-AAF in the cells occurs by this route. Freshly isolated cells activate N-OH-AAF to NOF as detected by high pressure liquid chromatography (HPLC). Cells frozen at-6 0C are more active. N-OH-AAF activation appears to be peroxidative since ascorbate and p-aminophenol completely inhibit NOF formation. Neither the acyl-transferase nor deacylase route occurs to any appreciable extent in the cells. Exogenously added arachidonate enhances N-OH-AAF activation and the inhibitor 5,8,11,14-eicosatetraynoic acid (ETYA) considerably decreased N-OH-AAF activation while indomethacin or aspirin were not effective. Ram seminal vesicle microsomes activate N-OH-AAF apparently by prostaglandin synthetase. Our work indicates that N-OH-AAF was activated by lipoxygenase pathway in these cells. The 12L-hydroperoxy-5,8,10,14-icosatetraenoic acid (12-HPETE) generated through endogenous or exogenous arachidonate sources probably is the hydroperoxide substrate for the peroxidase. Platelets which are rich in lipoxygenase also activate N-OH-AAF. Since 12-HPETE is one of the three hydroperoxides found in animal kingdom, the peroxidase activation may have significant importance in mammary gland carcinogenesis. (no Refs)

OTHER FUSED RING AMINES

14. STRUCTURAL BASIS OF THE MUTAGENICITY IN BACTERIA OF NITRATED NAPHTHALENE AND DERIVATIVES.

McCoy EC, Rosenkranz EJ, Petrullo LA, Rosenkranz HS, Mermelstein R
Center for Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Environ Mutagen; 3(5):499-511 1981

The mutagenic activity of nitronaphthalenes and some of their derivatives was investigated in the Salmonella mutagenicity assay. The 2-nitro and 2-hydroxylaminonaphthalenes were more mutagenic than their corresponding 1-substituted analogs.

The adducts induced by 1-nitronaphthalene differed chemically from those derived from the 2-nitro analog. For expression of the mutagenic action of these chemicals, reduction of the chemicals to the corresponding hydroxylamines was required. These differences in mutagenic responses may be due to the different DNA adducts that have been identified after reaction of hydroxylaminonaphthalenes with DNA. The nitroso-containing polycyclic chemicals might not derive their mutagenic activity from reduction to the corresponding hydroxylamines. If there is a relationship between mutagenicity in Salmonella and human risks, adjusting the conditions for combustion in engines such that extensive nitration is favored may decrease the emission of hazardous substances. On a molar basis, when a mutagen is capable of inducing frameshift mutations by adduct formation as well as by simple intercalation, then the activity induced by the adduct greatly exceeds the activity due to simple intercalators. While bicyclic 2-nitronaphthalene and 4-nitroquinoline-1-oxide and their metabolites are primarily base-substitution mutagens, the introduction of a third ring structure results in a different mutational mechanism leading to frameshift mutagens. (58 Refs)

15. EFFECT OF PH ON THE NEOPLASTIC TRANSFORMATION OF NORMAL HUMAN SKIN FIBROBLASTS BY N-HYDROXY-1-NAPHTHYLAMINE AND N-HYDROXY-2-NAPHTHYLAMINE.

Oldham JW, Kadlubar FF, Milo GE
(c/o Milo) The Comprehensive Cancer Center, Ohio State Univ., 410 West 12th Ave., Columbus, OH, 43210
Carcinogenesis; 2(9):937-940 1981

Normal human neonatal foreskin fibroblasts were treated with 2.0 ug/ml N-hydroxy-1-naphthylamine (N-HO-1-NA) and N-hydroxy-2-naphthylamine (N-HO-2-NA) (dose reducing the cloning activity by 50%). Treatment with N-HO-1-NA and N-HO-2-NA at culture medium pH of 5.0 induced colony formation at frequencies 3.3-6.9x and 4.0-4.1x greater, respectively, than those recorded at pH of 7.0. Injection of N-HO-1-NA- and N-HO-2-NA-transformed fibroblasts produced tumors in 1/8 and 2/7 nude mice, respectively. The findings indicate that acidic pH enhances the malignant transformation of normal cells exposed to N-hydroxy arylamines. Electrophilic metabolites of N-hydroxy arylamines may enter the cell, react with DNA, and induce neoplastic transformation. (20 Refs)

16. GRANULOCYTIC LEUKEMIA IN RATS: A REPORT OF TWO CASES.

Heath JE
Dept. Pathology, Coll. Medicine, Univ. Arkansas Medical Sciences, Little Rock, AR, 72201
Lab Anim Sci; 31(5):504-506 1981

Granulocytic leukemia was diagnosed in two male rats of different strains from 1,540 rats examined. The animals examined were from several different experiments involving chemicals or food additives and included control and treated rats. Although both rats with the disease had been treated with 2-naphthylamine or its hydroxy derivative, the significance of these chemicals in its induction is unknown. (Author abstract) (18 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

17. THE EFFECTS OF PRE-INCUBATION PERIOD AND NONHARMAN ON THE MUTAGENIC POTENCY OF 4-DIMETHYLAMINOAZOBENZENE AND 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE IN S. TYPHIMURIUM.

Lefevre PA, Ashby J
Central Toxicology Lab., ICI Ltd., Alderley Park, Macclesfield, Cheshire, England
Carcinogenesis; 2(9):927-931 1981

The mutagenic activities of liver carcinogens 4-dimethylaminoazobenzene (DAB) and 3'-methyl-4-dimethylaminoazobenzene (MeDAB) were tested using the Ames Salmonella typhimurium assay. Pre-incubation for 60 min produced a dose-dependent potentiation of DAB and MeDAB mutagenicity. The co-mutagen nonharman potentiated the mutagenic activity of DAB and MeDAB in direct plate assay (without pre-incubation). A 60-min preincubation in the presence of nonharman attenuated of mutagenic activity. (17 Refs)

18. PROSTAGLANDIN SYNTHETASE MEDIATED ACTIVATION OF P-DIMETHYLAMINOAZOBENZENE (BUTTER YELLOW) (MEETING ABSTRACT).

Vasdev S, Tsuruta Y, O'Brien P
Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The oral administration of dimethylaminoazobenzene (DAB) induces rodent liver tumors, mouse lung tumors and dog bladder tumors. It is believed that the activation by the liver of DAB involves liver microsomal mixed function catalyzed sequential N demethylation and N hydroxylation reactions. A cytosolic sulfotransferase then catalyzed the conjugation of the N-OH derivative with sulfate to form an electrophilic species which can bind to nucleic acids and protein. This electrophile is considered to be the ultimate carcinogenic metabolite. An alternative metabolic activation should now be considered. It has been found that prostaglandin synthetase can catalyze the binding of C14 DAB to microsomal protein. Extensive N demethylation occurred and C14 4-methylaminoazobenzene was much more effective at binding to the protein than DAB. Arachidonate was also more effective than NADPH with mouse lung and dog bladder microsomes. Cumene hydroperoxide was also much more effective than NADPH with rat liver microsomes. However, cytochrome P 450 was the catalyst for the latter hydroperoxide reaction as in this case extensive 4'hydroxylation also occurred. (no Refs)

19. STRUCTURALLY DIVERSE HEPATOCARCINOGENS IN VITRO INDUCE DRUG RESISTANCE IN RAT HEPATOCYTES WHEN TESTED IN VITRO (MEETING ABSTRACT).

Carr BI
Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA, 91010
Br J Cancer; 43(5):731 1981

Carcinogen-altered cells have generally been shown to be more resistant to the toxic effects of carcinogens than normal cells. It was therefore reasoned that the marked resistance of human hepatocellular carcinoma to cytotoxic chemotherapy might also be due to a carcinogen-induced phenotypic change in hepatocytes, resulting in an increased resistance to both carcinogen- and chemotherapy-mediated cytotoxicity. Male F344 rats were fed a basal diet and given aflatoxin B1 (AFB1) 30 ug daily ip or a basal diet containing either ethionine or 3'-methyl-4-dimethylaminoazobenzene. Rats were sacrificed weekly and their hepatocytes were placed in primary monolayer culture. Following a 3 hr attachment hepatocytes were exposed for 24 hr to Adriamycin (1.8x10-4M) cycloheximide (7x10-3M) or AFB1 (10-6M). Resistance was defined as the percentage of attached cells excluding trypan blue compared to untreated controls. Each of the 3 carcinogens induced greater than 50% resistance to AFB1 in the isolated hepatocytes after one wk, and comparable resistance to cycloheximide and Adriamycin after 4 wk. Hepatocytes from normal rats did not survive these concentrations of test drugs. In vivo, 3 different hepatocarcinogens induced marked resistance in rat hepatocytes to the potent carcinogen AFB1, as well as to the cytotoxic drug Adriamycin, using an in vitro assay, several mo before the appearance of hepatocellular carcinoma. Clinical drug resistance may be an early carcinogen-induced phenotype in primary tumors. (3 Refs)

20. MUTAGENICITY IN SALMONELLA OF DYES USED BY DEFENCE PERSONNEL FOR THE DETECTION OF LIQUID CHEMICAL WARFARE AGENTS.

Nestmann ER, Kowbel DJ, Wheat JA
Environmental Health Centre, Tunney's Pasture, Ottawa, Ontario, K1A OL2, Canada
Carcinogenesis; 2(9):879-883 1981

Six indicator dyes capable of detecting chemical warfare agents in liquid form were tested for mutagenicity in the Salmonella typhimurium/rat microsome plate incorporation assay. Ethyl-bis(2,4-dinitrophenyl)acetate, Orasol Navy Blue 2RB (TD-4), and Eastman Fast Blue G-BLF induced dose-related increases in His+ reversion mutations in three or more of the S typhimurium tester strains (TA153, TA100, TA1537, TA1538, and TA98). Papers in which the dyes were impregnated were also mutagenic. Thiodiphenyl-4,4'-diazo-bis-salicylic acid was weakly mutagenic in the plate assay but strongly mutagenic in a fluctuation assay. Fluorescent Brilliant Yellow R and 2,5,2',5'-tetramethyltriphyenyl methane-4,4'-diazo-bis-beta-hydroxynaphthoic anilide were not mutagens. (16 Refs)

HETEROCYCLIC AMINES

21. ANALYTICAL AND BIOLOGICAL ANALYSES OF TEST MATERIALS FROM THE SYNTHETIC FUEL TECHNOLOGIES. IV. STUDIES OF CHEMICAL STRUCTURE-MUTAGENIC ACTIVITY RELATIONSHIPS OF AROMATIC NITROGEN COMPOUNDS RELEVANT TO SYNFUELS.

Ho CH, Clark BR, Guerin MR, Barkenbus BD, Rao TK, Epler JL
Analytical Chemistry Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 85(5):335-345 1981

Mutagenicity of model compounds of aromatic nitrogen compound classes found in or possibly present in synfuel products was studied. Salmonella typhimurium tester strains TA1535, TA1537, TA1538, TA98, and TA100 were employed. Aromatic hydrocarbons with 1-4 rings produced no mutagenicity but 5-ring compounds (such as perylene and benzo(a)pyrene) exhibited significant mutagenicity. Most N-heterocyclics of from 1-4 rings produced no mutagenicity; 5-ring members like 1,2,7,8-dibenzacridine and 10-azobenzo(a)pyrene showed high activities while 2,2'-bipyridine and quinoline showed only slight activities. Presence of nitrogen may increase mutagenicity slightly but is not as important as the number of fused rings. Effects of amino and nitro groups substituted on the aromatic ring and of compounds containing 1 N atom in the ring and 1 amino substituent are also presented. Amino substituents have a significant effect in N-heterocyclic parent compounds. Multi-ring aromatic amines give a definite activity for a particular isomer whether the amino functional group is primary, secondary, or tertiary. Observed trends are discuss ed with reference to molecular structural features. (16 Refs)

22. ADDUCTS FROM THE REACTION OF O,O'-DIACETYL OR O-ACETYL DERIVATIVES OF THE CARCINOGEN 4-HYDROXYAMINOQUINOLINE 1-OXIDE WITH PURINE NUCLEOSIDES.

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Cancer Res; 41(11,part1):4559-4565 1981

The diacetyl derivative of 4-hydroxyaminoquinoline 1-oxide (4-HAQO), the proximate carcinogen of 4-nitroquinoline 1-oxide, was reacted in vitro with purine nucleosides to give five adducts (3 with guanosine and 2 with adenosine). The same nucleoside modifications were also obtained with a monoacetyl derivative of 4-HAQO which is probably 4-acetoxy-aminoquinoline 1-oxide. The structure of the major adduct (the so-called dG III) was identified as N-(deoxyguanosine-C8-yl)-4-aminoquinoline 1-oxide. The isolation of this adduct from the 4-HAQO-modified DNA in vivo provides strong support for the hypothesis that the acetyl derivatives of 4-HAQO constitute a good model for the ultimate carcinogen. (Author abstract) (21 Refs)

23. INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER BY PYROLYSIS PRODUCTS OF AMINO ACIDS.

Tamano S, Tsuda H, Tatematsu M, Hasegawa R, Imaida K, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 72(5):747-753 1981

The activities of pyrolysis products for initiating or promoting preneoplastic lesions were tested. In experimental series I, N-2-fluorenylacetamide (2-FAA) was used as a initiator or a promoter and 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1), 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) or 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2) was administered at a fixed dose and for the same period in the initiation stage or the promotion stage. Animals were subjected to partial hepatectomy or treated with carbon tetrachloride (CCl_4) to increase the induction of gamma-glutamyl transpeptidase (gamma-GT) positive foci. Trp-P-1 and Glu-P-2 administered in either the initiation or promotion stage significantly increased the induction of gamma-GT positive foci (p less than 0.001). Glu-P-1 increased the induction of gamma-GT positive foci (p less than 0.001) when administered in the initiation stage but it was not effective when administered during the promotion stage. In experimental series II, animals were given a single dose of these chemicals at one of the three different dose levels with partial hepatectomy and then were fed with 2-FAA and given a single dose of CCl_4. Trp-P-1, Glu-P-1 and Glu-P-2 caused dose-dependent inductions of gamma-GT positive foci. (Author abstract) (14 Refs)

24. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

U. S. GOVERNMENT PRINTING OFFICE : 1982—361-547/112

REVIEWS AND OTHER RELATED STUDIES

25. OCCUPATIONAL CANCER: PROBLEMS AND TASKS OF MEDICAL PRACTICE.

Konetzke GW
Zentralinstitut fur Arbeitsmedizin der DDR, Noldnerstrasse 40-42, 1134 Berlin, E. Germany
Z Aerztl Fortbild (Jena); 75(11/12):529-531 1981

The problems of occupational cancer and its prevention are discussed. Aside from ionizing radiation, asbestos and chemical substances are the most important carcinogenic factors in the working environment. The number of industrial chemicals with demonstrated or probable carcinogenic effect is only 30-40. They include aminodiphenyl, arsenic, asbestos, auramines, benzene, benzidine, technical chloromethylmethylether, chromium, 2,2-dichlorodiethyl sulfide, dichlorodimethylether, beta-naphthylamine, nickel, tars, mineral oils, ad vinyl chloride. Aflatoxins, acrylonitrile, beryllium, polychlorinated biphenyls, cadmium, dimethylcarbonylchloride, dimethylsulfate, ethyl oxide, and carbon tetrachloride are probable carcinogens. Occupational exposure to asbestos was definitely established in 303/743 patients with malignant mesothelioma, and occupational exposure was probable in 70. The prevention of occupational cancer includes the limitation of the use and production of carcinogenic substance to the extent absolutely necessary technologically, ban on especially hazardous carcinogens, compliance with occupational safety measures and hygienic standards, and check-up and monitoring of workers who have ever been exposed to carcinogenic factors. (7 Refs) (In GER)

26. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

This review deals with premalignant liver lesions in rats fed N-2-acetylaminofluorene (AAF) or diethylnitrosamine (DEN), DNA alterations in premalignant lesions, and cellular responses to skin tumor promotors such as tetradecanoylphorbol acetate (TPA). Rats fed four cycles of AAF exhibited persistent hepatic nodules having increased mitotic activity and altered DNA. Similarly, premalignant lesions induced by DEN and phenobarbital showed an increase in altered DNA, which paralleled the increase in risk of hepatoma. The broad effects of tumor promotion consist of the induction of proliferation of an initiated cell population and the appearance of aggregates of altered cells. Tumor promotors such as TPA heighten the mitotic responses in these cells and eventually induce epigenetic programmatic alterations. (38 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.
Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
In GER

9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.
Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.
Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.
Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

5. EPIDEMIOLOGY.
Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.
Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
In GER

18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.
Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.
Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.
Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.
Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

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28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.
Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.
Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/04

APRIL, 1982

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ANILINES AND EXTENDED ANILINES

1. CHRONIC TOXICITY AND RISK ASSESSMENT IN MICE EXPOSED TO BENZIDINE DIHYDROCHLORIDE (MEETING ABSTRACT).

Littlefield NA, Nelson CJ, Schieferstein G
National Center for Toxicological Research, Jefferson, AR
Toxicologist; 1(1):129 1981

Benzidine, recognized as a bladder carcinogen in man and as a liver carcinogen in experimental animals, is the chemical basis of as many as 200 commercial dyes. It has recently been demonstrated that physiological processes can metabolize these dyes to release benzidine, thereby creating a potential exposure hazard. To assess this hazard, both sexes of F1 hybrid (homogeneous) and F2 (heterogeneous) mice from a BALB/c male and C57BL/6 female cross were exposed for their respective live spans to benzidine dihydrochloride in their drinking water at concentrations of 0, 30, 40, 60, 80, 120, and 160 ppm for males and 20, 30, 40, 60, 80, and 120 ppm for females. Animals were removed from the study only when they were dead or moribund. This study was terminated after 33 mo of exposure. Using the endpoint of hepatocellular adenomas and carcino-

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mas, the Armitage-Doll multistage model was used to describe the tumor rates in the experimental dose range and obtain the upper confidence level on tumor rates. Linear interpolation was used between 0 dose and the upper confidence level of the lowest experimental dosage for predicting potential low dose tumor rates. Dose response effects on body wt, survival, and liver neoplasms were noted in both strains. For each of the endpoints, the females were more susceptible than males and the F1 (homogeneous) strain was more susceptible than the F2 (heterogeneous) strain. The calculated virtually 'safe' dose predicted to produce less than one per million F1 female mice with a liver tumor is 0.04 ppb. One ppb of benzidine dihydrochloride in the drinking water of these mice would theoretically produce liver tumors in less than 2.49 mice per 100,000 population. (no Refs)

2. EFFECTS OF CARCINOGENS, MUTAGENS, AND TERATOGENS ON NON-HUMAN SPECIES-AQUATIC ANIMALS (MEETING ABSTRACT).

Couch JA, Schoor WP
United States Environmental Protection Agency, Gulf Breeze, FL
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Aquatic systems and organisms are under both laboratory and field study in order to develop indicator, screening, and modeling capabilities for detection and evaluation of risks of carcinogens, mutagens, and teratogens. In the third yr of the program, several advances were made in the development of minnow (liver lesions via benzidine and aflatoxin exposures), rainbow trout (liver tumors via benzo(a)pyrene (B(a)P) exposures), and freshwater catfish (papillomatous-like lesions via chlorinated effluent exposures). A novel approach has shown that tiger salamanders may be good biochemical and histologic indicators of the presence of certain carcinogens (polycyclic aromatic hydrocarbons-PAH's). The skin and liver tissues of the salamanders revealed induced enzyme activity following exposure to the PAH, perylene. Considerable field monitoring work on mollusks and carcinogenic PAH's along the coast of Oregon has revealed a positive correlation between prevalence of cellular proliferation disorders in shellfish and higher concentrations of certain PAH's in natural water. Emphasis in biochemistry for the last yr has been directed mostly toward the elucidation of the metabolisms of the mixed-function oxidases in marine organisms. From continuing work on the mullet (Mugil cephalus), we have found that benzo(a)pyrene is converted mainly to 3-hydroxybenzo(a)pyrene, 9-hydroxybenzo(a)pyrene and 4, 5-,7,8-,9,10-dihydroxydiols of B(a)P, in in vitro systems containing liver microsomes from Aroclor 1254-treated mullet. Other metabolites such as diones of B(a)P and probably tri- and tetraols have also been produced. We have also developed a procedure for the epoxide hydrolase enzyme system in order to determine the role of this enzyme on the metabolism of the polyaromatic hydrocarbons. These studies continue to reveal that fish have similar metabolic pathways to mammals for disposition of certain carcinogens. (no Refs)

3. RESIDUAL BENZIDINE IN IMPORTED AND DOMESTIC BENZIDINE DYES.

Boeniger MF, Stein HP, Choudhary G, Neumeister CE
Natl. Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Toxicol Lett; 9(4):415-420 1981

The benzidine levels in 33 samples of dyes imported from 8 countries and in 26 samples of domestic dyes were analyzed by high pressure liquid chromatography. Results for imported dyes ranged from less than 1 ppm benzidine (direct blue 2 from Poland and direct red 28 from Korea) to 1254 ppm benzidine (direct black 38 from Egypt), with an av value of 64 ppm and a standard deviation of 219 ppm. Values for domestic dyes ranged from 1 ppm to 270 ppm with an av value of 16 ppm and a standard deviation of 52 ppm. Although a significant difference between imported and domestic dyes was not found, the imports do appear to contain more residual benzidine; such benzidine levels are possibly due to incomplete dye synthesis. Discontinuation of production of all benzidine based dyes has been recommended by the National Institute for Occupational Safety and Health. However, due to inadequate testing, it is further recommended that worker exposure to substitute dyes also be minimized. (17 Refs)

4. THE EFFECT OF DISULFIRAM ON THE CARCINOGENICITY OF 3,2'-DIMETHYL-4-AMINOBIPHENYL IN SYRIAN GOLDEN HAMSTERS AND RATS.

Fiala ES, Weisburger JH, Katayama S, Chandrasekaran V, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 2(10):965-969 1981

Species differences in 3,2'-dimethyl-4-aminobiphenyl (DMAB) carcinogenicity, which induces mostly bladder tumors in Syrian hamsters and intestinal and breast tumors in rats, were investigated. Groups of male Syrian golden hamsters received sc injections of DMAB weekly for up to 22 mo (total av cumulative dose 555 mg) either alone or simultaneously with disulfiram in the diet. At the tolerated dose of disulfiram (2.5 mg/kg), the overall tumor yield induced by DMAB alone was not affected, but the number o f small intestine tumors was reduced and the appearance of bladder and colon cancers was delayed. In two groups of male Charles River rats, weekly sc injection of DMAB (20 mg/kg) for 37 wk (total av cumulative dose 289 or 241 mg) induced primarily intestinal cancers. As in hamsters, addition of disulfiram to the diet of the second group reduced the incidence of small intestine cancers but resulted in the appearance of a small number of bladder cancers. DMAB-treated rats also developed in situ prostatic carcinoma, regardless of whether they were treated with or without disulfiram. (19 Refs)

5. INHIBITORY EFFECT OF 4,4'-DIAMINODIPHENYLMETHANE ON LIVER, KIDNEY AND BLADDER CARCINOGENESIS IN RATS INGESTING N-ETHYL-N-HYDROXYETHYLNITROSAMINE OR N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE.

Fukushima S, Hirose M, Hagiwara A, Hasegawa R, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Carcinogenesis; 2(10):1033-1037 1981

Effects of 4,4'-diaminodiphenylmethane (DDPM) in the 'post-initiation' stage of liver, kidney, and bladder carcinogenesis induced in male F344 rats by N-ethyl-N-hydroxyethylnitrosamine (EHEN) or by N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) were investigated. Rats given 0.1% EHEN in drinking water for 2 wk followed by DDPM treatment (0.1% in diet, 32 wk) had significantly fewer renal neoplastic nodules (av 0.28/square cm [cm2]) and renal cell tumors (av 0.16/cm2) than rats treated with EHEN alone (1.88 neoplastic nodules and 0.51 renal cell tumors/cm2). DDPM did not inhibit development of hyperplastic nodules in the liver. However, hepatocellular carcinomas did not occur in rats treated with EHEN and DDPM, whereas they were observed in 7/21 rats treated with EHEN alone. DDPM (0.1% in diet, 34 wk) also reduced the frequency of bladder papillomas induced by 4 wk or BBN treatment (0.01% in drinking water). In these experiments, rats treated with DDPM showed growth retardation and decreased food intake. (25 Refs)

6. RE-EVALUATION OF THE MUTAGENIC EFFECTS OF THE HAIR DYE P-PHENYLENEDIAMINE (BASE) IN THE SEX-LINKED RECESSIVE LETHAL TEST IN DROSOPHILA MELANOGASTER.

Blijleven WG

Dept. Radiation Genetics, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 90(2):137-141 1981

Results obtained with a purified sample of p-phenylenediamine in the Drosophila sex-linked recessive lethal test indicate that the compound is without mutagenic effect in this system. The only effect on treated males appears to be sterilization and toxicity. The findings contradict previous results, which could have reflected impurities not accounted for in the initial testing. (5 Refs)

7. THE EFFECT OF DIMETHYLSULFOXIDE ON THE MUTAGENICITY OF THE HAIR DYE P-PHENYLENEDIAMINE.

Burnett C, Fuchs C, Corbett J, Menkart J

Clairol Res. Laboratories, Stamford, CT, 06902

Mutat Res; 103(1):1-4 1982

Mutagenicity of p-phenylenediamine was examined in the Ames test. Choice of solvents and tight controls were shown to be important. Aqueous and fresh soln in dimethylsulfoxide were non-mutagenic; however, on standing at room temperature for 4 hr, the latter soln became highly active. (11 Refs)

8. CHRONIC DERMAL TOXICITY OF EPOXY RESINS. 1: SKIN CARCINOGENIC POTENCY AND GENERAL TOXICITY.

Holland JM, Gipson LC, Whitaker MJ, Eisenhower BM, Stephens TJ

Oak Ridge Natl. Lab., Oak Ridge, TN

Sci Tech Aerosp Rep; 19(20):2818 1981

This report quantifies the cutaneous and systemic response of male and female C3H mice to skin application of selected commercial epoxy resins and amine curing agents, at the max tolerated dermal dose. Resins tested were: diglycidyl ether of bisphenol A (DGEBA); mixtures of the same resins with bis(2.3-epoxycyclopentyl) ether; diglycidyl ether of resorcinol; N,N'-diglycidyl-5,5-dimethylhydantion; diglycidyl ether of neopentyl glycol; A 70:30 mixture of the hydantoin and neopentyl glycol base resins; the amine curing agent methane diamine and a dutectic mixture of meta-phenylenediamine and DGEBA. A DGEBA manufactured by Union Carbide Corporation in the mid 1970's and assayed for skin carcinogenicity previously was chemically characterized. The results of this analysis are included with the present data for comparison purposes. (no Refs)

9. 3-AMINOBENZAMIDE STIMULATES UNSCHEDULED DNA SYNTHESIS AND REJOINING OF STRAND BREAKS IN HUMAN LYMPHOCYTES.

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Biochemical Inst. B, Panum Inst., Univ. Copenhagen, Copenhagen, Denmark

Biochem Biophys Res Commun; 102(4):1254-1261 1981

The effects of 3-aminobenzamide (3AB) on DNA repair in human lymphocytes, L1210 cells, and sarcoma 180 ascites cells were examined by measuring both unscheduled DNA synthesis and the rejoining of strand breaks. 3AB (3 milliM) stimulated unscheduled DNA synthesis, as measured by 3H-thymidine incorporation, in UV-irradiated and dimethylsulfate (DMS)-treated human lymphocytes. At a similar concentration (2.5 milliM), this compound also stimulated the rejoining of DMS-induced strand breaks, as measured by alkaline elution procedures. In contrast, 3AB inhibited DNA repair in similarly treated L1210 and sarcoma 180 ascites cells. The effects of another inhibitor of poly(ADP-ribose) synthesis, nicotinamide, were similar to those of 3AB, indicating that there is a relationship between DNA repair and poly(ADP)ribose synthesis in these cell types. (12 Refs)

10. CONTRIBUTION OF INCORPORATED 5-BROMODEOXYURIDINE IN DNA TO THE FREQUENCIES OF SISTER-CHROMATID EXCHANGES INDUCED BY INHIBITORS OF POLY-(ADP-RIBOSE)-POLYMERASE.

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Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Sylvius Lab., Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 84(1):125-132 1981

The role of 5-bromodeoxyuridine (BrdUrd) incorporated into DNA on sister-chromatid exchanges (SCE) induced by inhibitors of poly-(ADP-ribose)-polymerase (PARP) was studied in Chinese hamster ovary (CHO) cells. Cells were grown in medium containing 5 uM BrdUrd to produce sister chromatids containing bifiliarly (BB) or unifiliarly (TB) substituted DNA. Other cultures were exposed to BrdUrd followed by thymidine (TdR) to produce unifiliarly substituted (TB) or unsubstituted (TT) DNA. Exposure to 3-aminobenzamide (3-AB: 0-10 uM) induced SCE in a dose-dependent manner (6.45-54.10 SCE/cell). Benzamide (BA) also produced dose-dependent SCE. Frequencies of SCE were doubled when 3-AB was present during the first cell cycle; the increase was six-fold when 3-AB was present during the second cell cycle. The increase was additive when 3-AB was present during both cycles. The DNA template used for replication, but not the presence of TdR or BrdUrd in the medium, was critical for induction of SCE. Both 3-AB and BA inhibited PARP. Results after reversal of DNA labeling patterns indicated that the presence of BrdUrd, rather than cell cycle number, was directly related to SCE. Mutations to HGPRT- were not increased by 3-AB or BA. Since 3-AB and BA produced SCE, but not point mutations, the SCE test may produce false positive results in mutagenicity tests. (13 Refs)

11. NEOPLASTIC TRANSFORMATION ASSAY WITH BALB/C 3T3 CELLS. ANALYSIS OF RESULTS WITH 70 CODED SAMPLES (MEETING ABSTRACT).

Sivak A, Lobb AM, Tu AS
Arthur D. Little, Inc., Cambridge, MA, 02140
Toxicologist; 1(1):131 1981

Exposure of certain populations of mouse BALB/c 3T3 cells to chemical carcinogens results in morphological transformation in the cell culture that can be identified and quantified. In the assay validation, 15 uncoded and 70 coded chemicals comprising a series of known carcinogens and noncarcinogens were tested using a standard protocol. Among the chemical classes tested, polycyclic aromatic hydrocarbons, direct-acting alkylating agents, activated aromatic amine metabolites and certain metal carcinogens gave positive responses. Aromatic amines, nitrosamines and other chemicals, such as natulan and cyclophosphamide, that require metabolic activation to exhibit activity, did not induce neoplastic transformation, although aniline was positive. The hormones ethynylestradiol, progesterone and diethylstilbesterol, which are likely epigenetic carcinogens, were not active in this system. Statistical analyses of the data reveal that: (1) the range of spontaneous transformation frequency has a mean value of 0.28 foci/plate; (2) the induced transformation frequency of the positive control (3-methylcholanthrene, 2 ug/ml) has a mean value of 2.6 foci/plate; (3) at control values above the cumulative mean, a doubling of transformation frequency in treated cultures is a statistically significant positive effect (alpha less than or equal to 0.05). At the control values below the cumulative mean, statistical significance is achieved only at higher treated to control response ratios, which rise sharply as control values approach zero. (4) The relationship of the untreated control response to the positive response is not a simple background incidence. (no Refs)

FLUORENAMINES: IN VIVO

12. INITIATION/PROMOTION ASSAY FOR CHEMICAL CARCINOGENS IN RAT LIVER (MEETING ABSTRACT).

Pereira MA, Herren SL, Britt AL, Khoury M
Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH, 45268
Toxicologist; 1(1):155 1981

We have developed a short-term initiation/promotion assay in rat liver for the detection of chemical carcinogens. Male rats (175-200 gm) were po administered the chemical under test. One wk later tumor promotion by 500 ppm sodium phenobarbital in the drinking water was commenced. After 8 wk of promotion the rats were sacrificed and the liver stained and scored for gamma glutamyl transpeptidase (GGTase) positive foci. The appearance of GGTase positive foci was taken as an indication of the initiation of carcinogenesis by the chemical. In some cases partial hepatectomy was performed 24 hr prior to the administration of the test chemical in an attempt to increase the sensitivity of the assay. Acetylaminofluorene (AAF), aflatoxin B1 (AFB1) benzo(a)pyrene (BaP), diethylnitrosamine (DENA), 7,12-dimethylbenzo(a)anthracene (DMBA), dimethylnitrosamine (DMNA), N-methyl-N'-nitro-N-nitrosoguaninidine and urethane were positive in the assay while benzene (30 mmole/kg) was apparently negative. Phenobarbital promoted the response of AAF, AFB, DENA, DMBA and DMNA. Partial hepatectomy 24 hr prior to initiation increased the response of AAF, BaP, DENA and DMBA. The initiation/promotion assay in rat liver that includes 1) partial hepatectomy at 24 hr prior to administering the test chemical, 2) phenobarbital promotion and 3) GGTase foci as indication of carcinogenic activity; would appear to be sensitive to a wide variety of chemical carcinogens. (no Refs)

13. CHEMICAL LIVER CARCINOGENESIS, MONITORING OF THE PROCESS BY FLOW CYTOMETRIC DNA-MEASUREMENTS (MEETING ABSTRACT).

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Institute of Pathology, Oslo 1, Norway
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The carcinogenic process in the liver was monitored from early non-neoplastic changes to the development of tumors in two well known models; giving Dimethylnitrosamine (DMN) ip to newborn mice, and feeding rats with Acetylaminofluorene (AAF). Liver parenchyma cells and liver tumor cells were isolated by collagenase treatment and prepared for flow cytometric (FCM) measurements of nuclear DNA content. The changes observed were correlated to morphology and 3H-thymidine incorporation. The early preneoplastic changes in hepatocytes from DMN-treated mice were shifts in the DNA content to classes of higher nuclear ploidies. AAF-feeding of rats caused gradual distortion of the DNA content of nuclei from parenchymal cells. After 16 wk of exposure, before any tumors were seen, a majority of the nuclei displayed an aneuploid DNA content. The significance of these changes in the carcinogenic process is discussed, and a possible use of these models for detection of hepatotrophic agents and agents causing aneuploidy (clastogens and turbagens) is proposed. The liver neoplasias (adenomas and hepatocellular carcinomas) induced by these models contained tumor stemlines with diploid DNA content, some hepatocellular carcinomas showed aneuploidy. Proliferative nodules contained diploid and tetraploid stemlines. (no Refs)

14. INCREASED ACTIVITY OF A NEUTRAL PROTEASE IN CYTOSOL FROM RAT HEPATOMA INDUCED BY N-2-FLUORENYLACETAMIDE.

Wada K, Matsui H, Tsukada K
(c/o Tsukada) Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Cancer Res; 41(12):5130-5133 1981

A protease active with N-alpha-benzoyl-DL-arginine-p-nitroanilide with an optimum pH of 7.3 has been found in the cytosol of rat liver. The activity of this protease increased in N-2-fluorenylacetamide-induced hepatoma as well as in fetal liver. It has been purified from normal liver and hepatoma about 200-fold. Its mol wt is estimated by gel filtration to be about 200,000 in each tissue. The protease activity is unaffected by chymostatin, pepstatin, soybean trypsin inhibitor, and p-chloromercuribenzoate. Antipain, leupeptin, tosyl-L-lysine chloromethyl ketone, and phenylmethylsulfonyl fluoride inhibit the protease activity. This protease appears to be a serine protease. (Author abstract) (22 Refs)

15. LIVER CELL MEMBRANE ALLOANTIGENS AS CELLULAR MARKERS IN GENOTYPIC MOSAIC RAT LIVERS UNDERGOING CHEMICALLY INDUCED HEPATOCARCINOGENESIS.

Hunt JM, Buckley MT, Onnink PA, Rolfe PB, Laishes BA
McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Cancer Res; 42(1):227-236 1982

We have developed a new marker system utilizing rat alloantigens as genetic cellular markers for hepatocytes in genotypic mosaic livers of rats undergoing hepatocarcinogenesis. This marker system has been designed to facilitate the eventual purification of subpopulations of hepatocytes from such livers which contain precursor cells of carcinomas. Thus, a lineage relationship between cells of early putative premalignant liver lesions and those of carcinomas may ultimately be established, and the process of cancer development may be biochemically probed. A donor-to-host liver cell transplantation procedure was used. Host rats subjected to a 2-acetylaminofluorene/partial hepatectomy regimen were grafted orthotopically iv with donor liver cells via a mesenteric vein of the hepatic portal system. Cryostat sections of host rat livers were prepared 10 to 13 days after donor liver cell transplantation for histochemical localization of gamma-glutamyltranspeptidase-positive (GT+) hepatocyte colonies Genotypic mosaic host rat livers were further analyzed by indirect immunofluorescence in serial cryostat sections to identify hepatocyte colonies on the basis of their strain-specific alloantigens. Polyvalent F344 anti-WF alloantiserum was prepared by immunizing F344 rats with WF skin and spleen cells. The resulting serum reacted positively by indirect immunofluorescence with cryostat liver sections as well as collagenase-dissociated hepatocytes from WF and WF x F344F1 hybrid rats. No reaction of the alloantiserum with F344 liver tissue or isolated hepatocytes was observed. Some F344 donor origin colonies did not express the GT+ phenotype and were classified as gamma-glutamyltranspeptidase-negative. With the aid of tissue architectural landmarks, 276 individual colonies were analyzed. Ninety-seven per cent of the colonies appeared to be of F344 donor origin (92% FA- GT+; 5% FA- gamma-glutamyltranspeptidase-negative); 3% were FA+ GT+; and apparently of F1 hybrid host origin. Rat alloantigens expressed on the surface of hepatocytes may offer the potential for purification of donor-origin putative premalignant hepatocytes from genotypic mosaic host rat livers at sequential stages of hepatocarcinogenesis. (31 Refs)

16. RESISTANCE TO THE CYTOCIDAL EFFECTS OF ADRIAMYCIN IS AN EARLY PHENOTYPIC CHANGE INDUCED DURING HEPATOCARCINOGENESIS.

Carr BI, Laishes BA
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Br J Cancer; 44(4):567-571 1981

Resistance to the cytocidal action of Adriamycin (ADR) was induced in rat hepatocytes by incorporation of the carcinogen 2-acetylaminofluorene into the rat diet. Using a quantitative assay in primary monolayer culture, it was demonstrated that resistance to ADR is an early phenotypic change that is induced during chemical carcinogenesis in the rat, and appears to be stable. (Author abstract) (20 Refs)

17. THE EFFECT OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF THE HEPATOCARCINOGEN 2-ACETYLAMINOFLUORENE IN THE RAT.

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University of Southern California, Los Angeles, CA, 90007
Diss Abstr Int [B]; 42(4):1412-B 1981

Hepatic enzymes, presumably involved in the metabolism of the hepatocarcinogen 2 -acetylaminofluorene (AAF), were examined in rats fed a Torula yeast-based selenium-deficient diet or the same diet supplemented with 0.5 ppm selenium (as sodium selenite). Selenium-deficient rats exhibited almost total absence of hepatic selenium-dependent glutathione peroxidase activity three wk after initiation of test diet feeding. Dietary selenium had no significant effect on hepatic soluble sulfotransferase activity in vitro as measured with the substrates, N-hydroxy-AAF and phenol. Hepatic lipid peroxidation (HLP) was not altered by AAF-challenge in rats fed either diet. In agreement with previous reports, dietary selenium protected against increased HLP produced by administration of carbon tetrachloride. Selenium-supplemented rats exhibited (a) no significant change in the production of 7-,5-, and N-hydroxy-AAF metabolites and (b) significantly increased production of 3-hydroxy-AAF metabolite as compared to selenium-deficient rats. Dietary selenium had no significant effect on total metabolites excreted or on the major phenolic metabolites excreted into the free-glucosiduronic acid-conjugated, or sulfuric acid-conjugated fractions. However, selenium-deficient rats excreted two and three x more N-hydroxy-AAF into the free-, and glucosiduronic acid-conjugated fractions, respectively. These findings tend to support the hypothesis that dietary selenium alters the in vivo metabolism of AAF in a manner that selectively decreases N-hydroxy-AAF excretion, and possibly its production. Thus dietary selenium's protective effect against AAF-induced hepatocarcinogenesis may be partially explained by the ability of selenium to decrease the amount of N-hydroxy-AAF available for further activation. (no Refs)

18. EFFECTS OF PROMOTERS ON N-BUTYL-N-(4-HYDROXYBUTYL) NITROSAMINE INDUCED BLADDER CARCINOGENESIS IN THE RAT (MEETING ABSTRACT).

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Nagoya City University Medical School, Nagoya 467, Japan
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Male F344 rats were initially given 0.01% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) for 4 wk in drinking water followed by the feeding of diet containing various chemicals for 32 or 34 wk. In the groups of animals subjected to sodium saccharin, sodium ascorbate, D,L-tryptophan and allopurinol, there was a significant increase in the incidence and number of papillary or nodular hyperplasias (PNH) compared to the groups given BBN alone. However, these compounds did not enhance the induction of papillomas which were generally considered to be more advanced lesions. Experiments were done to determine whether treatment with sodium saccharin or phenobarbital could enhance the neoplastic lesions in the bladder or liver of rats pretreated with 2-acetylaminofluorene (2-AAF) or BBN for initiation. Male Fischer 344 rats were given 0.05% phenobarbital and 5.0% sodium saccharin, respectively for 32 wk after 4 wk administration of hepatocarcinogenesis. Sodium saccharin significantly enhanced the induction of PHN in the bladder, but not of papillomas after BBN treatment, and significantly induced bladder hyperplasias after 2-AAF treatment.

However, after 2-AAF or BBN treatment, an effect of phenobarbital for bladder and of sodium saccharin for liver neoplasia induction was not observed. The data indicate that although 2-AAF and BBN have tumor-initiating effects in both liver and urinary bladder, the tumor-promoting effects of phenobarbital and sodium saccharin are organ specific. (no Refs)

19. AN EVALUATION OF THE DROSOPHILA ZESTE SOMATIC EYE MUTATION TEST FOR THE DETECTION OF GENOTOXIC AZO DYES AND AN AROMATIC AMINE.

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Mutat Res; 84(1):221-226 1981

As part of a program for the assessment of genotoxicity of two currently United Kingdom-listed amino-azo food colors Brown FK and Red 2G and its delisted structural analogue Red 10B, the zeste somatic eye mutation system was used as a potentially sensitive single generation assay requiring further validation as an alternative to the sex-linked recessive lethal assay. A modification facilitating the use of the test with dyes and an evaluation of its sensitivity to 2-acetylaminofluorene (2-AAF) and o-aminoazotoluene was also undertaken. The zeste somatic eye system was incapable of detecting the activity of 2-AAF. (28 Refs)

FLUORENAMINES: IN VITRO

20. SULFATE-DEPENDENT METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY PRIMARY CULTURES OF ADULT RAT HEPATOCYTES (MEETING ABSTRACT).

Spilman SD, Byard JL
Department of Environmental Toxicology, University of California, Davis, CA, 95616
Toxicologist; 1(1):35 1981

The role of sulfate in the metabolic activation of the model aromatic amine hepatocarcinogen 2-acetylaminofluorene (2AAF) was determined using primary hepatocyte cultures as a cellular model of the liver. Adult male rat hepatocytes were isolated by collagenase perfusion of the liver and maintained in collagen-coated dishes with hormone-supplemented, chemically defined media. Cytochrome P-450 levels were fully maintained in the cultures for 48 hr. After 28 hr, the cultures were incubated with 67-137 ng of [14C]2AAF. Polar metabolites were isolated by chloroform-water partitioning, and bound carcinogen residues were measured as non-extractable radioactivity incorporated into hepatocellular trichloroacetic-acid-insoluble material. In an experiment using sulfate-free medium, sulfate supplementation doubled the level of bound residues at 2 and 3 1/2 hr but had no effect at 21 hr . Culture media containing 0, 0.1, 0.5 and 1.0 mM sulfate respectively produced 0.8, 1.4, 3.6 and 4.8% bound residues in a 3 hr incubation. Sulfate supplementation did not effect the overall rate of 2AAF metabolism. Phenol, at 1 uM in sulfate-free media, doubled the level of bound residues. Galactosamine, at 2mM, reduced by half the level of bound residues in cultures incubated with 2AAF and 1mM sulfate. These findings support the importance of sulfoconjugation in the metabolic activation of 2AAF. (no Refs)

21. SPECIFICITY OF RABBIT PULMONARY CYTOCHROME P-450 ISOZYMES IN THE ACTIVATION OF SEVERAL AROMATIC AMINES AND AFLATOXIN B1.

Robertson IG, Philpot RM, Zeiger E, Wolf CR
Lab. Molecular Genetics, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Mol Pharmacol; 20(3):662-668 1981

The activation of 2-aminoanthracene (2-AA), 2-aminofluorene (2-AF), 2-acetylaminofluorene (2-AAF), and aflatoxin B1 (AFB1) by rabbit pulmonary and hepatic preparations was studied using the Salmonella strain TA98. In experiments with either antibodies to specific cytochrome P-450 isozymes or monooxygenase systems reconstituted from purified enzymes, the observed activities were related to the relative concentrations and activities of these isozymes. Rabbit pulmonary and hepatic S16 fractions produced mutagenic products from 2AA, 2AAF, and 2AF, and AFB1. The hepatic fraction was more active, with regard to the amount of S16 protein required to produce a given number of revertants, with 2AA (up to 2x), 2-AAF (2.5-5x), and AFB1 (5x), whereas the pulmonary fraction was more active with 2AF (up to 2x). On the basis of cytochrome P-450 content, the activity of the pulmonary fraction was greater than or equal to that of the hepatic fraction. For a given substrate concentration, a comparison of the amounts of cytochrome P-450 required for equivalent activity showed that the pulmonary microsomal fraction was 3-4, 20-25, and 25-30x more active than the hepatic fraction in the formation of mutagenic products from 2AAF, 2AA, and 2AF, respectively. With AFB1, similar activities were obtained with both microsomal fractions, the pulmonary fraction being slightly more active. The promutagens 2AA, 2AF, and 2AAF were substrates for both P-450II and P-450LM4 but were inactive with P-450I. P-450LM1 showed greater activity with 2AAF, however, P-450II gave 10-20 times more mutagenic activity with 2AA and 2AF than did P450LM4. With AFB1, only incubations containing P-450I gave a significant increase in the number of revertants. Experiments with antibodies against P-450I and P-450II confirmed these findings. (29 Refs)

22. HOT SPOTS OF FRAMESHIFT MUTATIONS INDUCED BY THE ULTIMATE CARCINOGEN N-ACETOXY-N-2-ACETYLAMINOFLUORENE.

Fuchs RP, Schwartz N, Daune MP
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Nature; 294(5842):657-659 1981

An important step in carcinogenesis is thought to be the initial attack of the DNA molecule by a so-called ultimate carcinogen. More than 90% of the carcinogens tested have been found to be mutagens in bacterial systems. The covalent binding of the ultimate carcinogen to the DNA bases or phosphate groups creates a premutational lesion that in vivo is processed by the repair, replication and recombination enzymes, and eventually may be converted into a mutation. Being interested in the way that an initial premutational event is converted into a stable heritable mutation, we have sequenced stable mutations in a gene that has formed covalent adducts in vitro with N-acetoxy-N-2-acetylaminofluorene (N-AcO-AAF, a model for the ultimate metabolite of the rat liver carcinogen 2-acetylaminofluorene AAF). We show here that the mutations are mainly frameshifts involving G-C base pairs, and that certain base pairs (hotspots) are affected at relatively high frequencies. These results fit a model in which N-AcO-AAF-modified guanine acts as a non-coding base that during replication results in deletion of the modified residue. (Author abstract) (23 Refs)

23. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS
Microbiological Associates, Bethesda, MD, 20816
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 C1 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

24. IN VITRO REACTION OF THE CARCINOGENIC DERIVATIVE N-ACETOXY-7-ETHYL-N-2-ACETYLAMINOFLUORENE WITH DNA. A SPECTROSCOPIC STUDY.

Saint-Ruf G, Spodheim-Maurizot M, Loukakou PE, Coic JP
Centre de Biophysique Moleculaire, CNRS, 1A, avenue de la Recherche Scientifique, F-45045 Orleans cedex, France
Carcinogenesis; 2(10):1019-1025 1981

Reaction in vitro of DNA with N-acetoxy-7-ethyl-N-acetylaminofluorene (N-AcO-EtAAF) was compared with N-acetoxy-N-acetyl-2-aminofluorene (NAcO-AAF). Introduction of an ethyl group at position 7 of the fluorene ring induces an increase of reaction of this (model) metabolite of the carcinogen 2-acetoxy-2-aminofluorene (2-AAF) toward DNA and its constituents. UV absorption and circular dichroism spectroscopic methods were used to characterize the DNA reacted with N-AcO-EtAAF (DNA-EtAAF). Results indicate some conformational similarities between native DNA-EtAAF and DNA-AAF such as the presence of destabilized regions around the bound carcinogen and of stacking interactions between these residues and the adjacent nucleotides. Important differences appear to exist between adducts or modified sequences in native as compared to denatured DNA (contrary to DNA-AAF and DNA bearing covalently bound 2-aminofluorene). (19 Refs)

25. IMMUNOCYTOLOGICAL DETECTION OF AAF-DNA ADDUCTS IN HELA CELL NUCLEI.

Sage E, Gabelman N, Mendez F, Bases R

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Cancer Lett; 14(2):193-204 1981

Rabbit antibodies for acetylaminofluorene (AAF)-guanosine and for DNA modified by the presence of AAF adducts were utilized. HeLa cells growing in suspension at 2.5 x 10(5)/ml were exposed to increasing concentrations of N-acetoxy-AAF in dimethylsulfoxide at less than 0.5% final concentration. Dose-dependent increase in the proportion of immunoreactive cells in cultures exposed to carcinogen for 15 min at 37 C was observed. When the time course of disappearance of nuclear immunoreactivity toward anti-AAF-DNA was compared with the loss of radiolabel in cells exposed to 5 ug/ml of labeled N-acetoxy-AAF, nuclear immunoreactivity was induced but then declined rapidly for 5 hr. The total radiolabel in purified nuclear DNA declined much more slowly. In the first 3 hr after removal of carcinogen, the induced immunoreactivity was rapidly lost with no significant reduction in labeled DNA or in the dominant adduct fraction, N-(deoxyguanosin-8-yl)-2-aminofluorene (dG-C8-AAF). In the next 3 hr loss of immunoreactivity was insignificant but the drop in acetylated C-8 adducts was dramatic. Radiolabel experiments indicated that most adducts were still within the nucleus but did not react with antibody. It is suggested that DNA-AAF adducts become inaccessible to antibody due to the mechanics of the repair process. (33 Refs)

26. CHARACTERIZATION OF DNA REPAIR ELICITED BY CARCINOGENS AND DRUGS IN THE HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST.

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J Toxicol Environ Health; 8(3):463-477 1981

Autoradiographic unscheduled DNA synthesis measured in the hepatocyte primary culture/DNA repair test after exposure to chemical carcinogens was characterized. Replicated and nonreplicated hepatocyte DNA was separated by CsCl gradient centrifugation. Uptake of 3H-thymidine into nonreplicated DNA was seen after exposure of hepatocytes to the activation-independent carcinogen methyl methanesulfonate or the activation-dependent carcinogen N-2-acetylaminofluorene, but not with fluorene, a noncarcinogen. N-4-acetylaminofluorene, a mutagen with uncertain carcinogenicity, also elicited DNA repair. Density gradient centrifugation allowed the detection of DNA repair in hepatocytes following exposure to the antihistamines pyrilamine maleate and tripelennamine HCl. Methapyrilene did not elicit repair. (44 Refs)

OTHER FUSED RING AMINES

27. A COHORT STUDY ON CANCER AMONG WORKERS EXPOSED TO AN ANTIRUST OIL.

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Dept. Occupational Medicine, Sahlgrenska Sjukhuset, S-413 45 Goteborg, Sweden
Scand J Work Environ Health; 7(3):179-184 1981

An epidemiologic study of workers in an engineering company was conducted following the observation of three cases of cancer among women who wrapped bearing rings covered with antirust oil. Group A (98 persons) worked in the same packing department as the three affected women between 1954 and 1957 and were exposed to white spirit, mineral oil, lanolin, zinc naphthenate, and N-phenyl-1-naphthylamine + sodium nitrite. Group B (33) worked in another packing department and were exposed to mineral oil, vaseline, and stearic acid + sodium nitrite. Group C (31) had been treated for eczema from antirust oil in 1955 and had been exposed to white spirit, mineral oil, lanolin, zinc naphthenate, and N-phenyl-1-naphthylamine. Twelve cancers were found only among the women in Group A (expected value was 3.9 cancers); four cancers each were found in Group B and C (expected values were 2 and 3.8, respectively). The cancers in Group A were in the colon, breast, collum of the uterus (4), ovary (2), bladder, brain, thyroid, and reticulosarcoma. Two workers in Group C developed cancer of the bladder, one of whom was also included in Group A. The most likely etiological agent for Group A cancers is N-phenyl-1-naphthylamine, either alone or in combination with sodium nitrite. (15 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

28. INDUCTION OF SKIN PAPILLOMAS IN THE SENCAR MOUSE AS A TIER 2 CARCINOGENESIS BIOASSAY (MEETING ABSTRACT).

Bull RJ, Robinson M, Glas J, Cmehil D, Orthoefer J
Health Effects Research Laboratory, Cincinnati, OH, 45268
Toxicologist; 1(1):129 1981

The Toxic Substances Control Act mandates the testing of industrial chemicals for which insufficient evidence of safety exists. One of the more critical areas in chemical carcinogenesis testing is a dependable approach to confirmatory tests (tier 2) of identifed positives at a screening level (tier 1). The present work was undertaken as part of a systematic evaluation of a series of short-term in vitro and in vivo tests which possess properties thought desirable for tier 2 testing. Experiments were designed to determine whether the mouse skin responds to initiating doses of carcinogens selected from the major carcinogen classes administered by four routes, oral, ip, sc and topical. Experiments to date include testing of diethylnitrosamine, urethane, benzene, benzo(a)pyrene, dimethylbenzanthracene (DMBA), aflatoxin B1, methylmethane sulfonate, azobenzene, FANFT and lead acetate. Two wk following application of the initiating doses of each carcinogen a 20 wk promotion schedule involving the application of 1 ug of 12-O-tetradecanoyl phorbol-13-acetate (TPA) was initiated. On the basis of preliminary data it is apparent that papilloma development in response to chemical carcinogens varies with route of exposure. For example, it is apparent that the response to urethane administered po exceeds that observed by the topical route by 3-fold. Conversely, the response of the mouse skin to benzo(a)pyrene is more than 10-fold by the topical vs systemic routes of exposure. Route specific responses to DMBA, benzene, diethylnitrosamine and aflatoxin B1 are also apparent. These results suggest that consideration be given to employing more than one route of exposure in testing of chemicals using the mouse skin initiation/promotion system. (no Refs)

29. CARCINOGENIC INITIATION AS OPPOSED TO COMPLETE CARCINOGENICITY IN THE RODENT LIVER (MEETING ABSTRACT).

Ashby J, Elliott BE, Lefevre P, Styles J
Imperial Chemical Industries PLC, Cheshire, England
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

It is known that 4-N-Pyrrolidinylazobenzene (4N) is a close structural analog of the rodent liver carcinogen 4-dimethylaminoazobenzene (DAB). This structural similarity led us to evaluate it for genotoxic activity in vitro. We observed activity for 4N and DAB in the BHK cell transformation assay and subsequently in the Salmonella mutation assay of Ames. By a curious chance, Scribner, Miller and Miller, probably prompted by the same structural similarity, had synthesized 4N in the 1960's and found it to be noncarcinogenic to the rodent liver using a bioassay test protocol that detected DAB as carcinogenic. These findings were only described following the publication of our observations made in vitro. The conflict that apparently exists between these data can be interpreted in two separate ways: a) Scribner et al have suggested that 4N may be a carcinogenic initiator as opposed to a complete carcinogen like DAB. They also suggested that promotion of 4N-treated rodents with phenobarbitone might lead to the production of liver tumors. b) We have evaluated the simpler concept that the activities observed for 4N in vitro define a carcinogenic potential that is not realized in vivo due to its rapid detoxification, at least in rodents. The first of these explantations implies that pure carcinogenic initiators may form a separate class of genotoxic agents from complete carcinogens and than 4N might provide a valuable model compound for the study of carcinogenic promotion in the rodent liver. The second explanation regards potential carcinogenicity as a single property that can be defined in vitro and which may or may not be expressed in vivo depending on the enzymic environments encountered by the test chemical. (no Refs)

30. ABNORMAL GLYCOSYLATION OF AFP DURING 3'MDAB HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Kelleher PC, Smith CJ, Schwartz CE, Chiu JF
Department of Medicine, University of Vermont, Burlington, VT, 05405
Oncodev Biol Med; AbstractsBook,1:36 1981

Chemically-induced hepatomas secrete alpha fetoprotein (AFP) which reacts differently with concanavalin A (ConA) than does AFP secreted by regenerating liver. We investigated binding to ConA of AFP secreted during 3'-methyl-4-dimethylaminoazobenzene (3'MDAB) hepatocarcinogenesis. 3'MDAB (0.06%) was fed continuously until either hepatomas developed or the rats were killed after predetermined time intervals between 7 and 165 days. AFP was measured immunochemically and ConA-binding characterized by affinity chromatography. Each result is the mean of 4 to 6 rats. Nineteen and 27 days after starting 3'MDAB feeding, 53 and 57% of serum AFP was ConA-nonbinding. Between 33 and 81 days the percent nonbinding AFP was stable, between 27 and 35% (6 sampling dates). Subsequently, the percentage of nonbinding AFP present at each sampling date rose to between 42 and 71%, fluctuating widely between sampling dates. Serial sampling of individual rats revealed a similar change in AFP binding to ConA during 3'MDAB feeding. Variations within animals was as great as the variation between animals. At no period of time during 3'MDAB feeding was the pattern of AFP binding to ConA similar to that during liver regeneration, indicating that the processing of AFP during hepatocarcinogenesis differs from that during liver regeneration. Altered AFP glycosylation is an early event in hepatocarcinogenesis. (no Refs)

31. ALTERED DYNAMICS OF ALPHA-FETOPROTEIN PRODUCTION FOLLOWING PYRIDOXINE AND ADENOSINE 5'-TRIPHOSPHATE ADMINISTRATION TO CIRRHOTIC PATIENTS WITH OR WITHOUT PRIMARY HEPATOMAS AND TO LIVER-INJURED AND HEPATOMA-BEARING RATS.

Watanabe A, Nagashima H

First Dept. Internal Medicine, Okayama Univ. Medical Sch., 2-5-1 Shikata-cho, Okayama 700, Japan

Oncodev Biol Med; 2(5):313-321 1981

Serum alpha-fetoprotein (AFP) levels were determined in 100 patients with liver cirrhosis. Of the 50 patients with cirrhosis and primary hepatomas, 35 had AFP levels higher than 10(4) nanog (ng)/ml. Serum AFP levels remained low (less than 200 ng/ml) in 8/50 patients with hepatomas, and in 5/50 in this group the levels were between 200 and 2,000 ng/ml. The highest AFP level found in patients with cirrhosis alone was 1,600 ng/ml. In 12 patients with chronic liver disease without clinical evidence of hepatoma and whom subsequently developed primary hepatomas over a 2 to 32 yr follow-up period, AFP levels were not useful for earlier detection. In rats with livers injured by CCl4, simultaneous injections of pyridoxine and adenosine 5'-triphosphate (ATP) resulted in significant decreases of elevated serum AFP levels. However, this treatment had no effect on the AFP levels in 3'-methyl-4-dimethylaminoazobenzene induced hepatoma-bearing rats. Ten men with cirrhosis followed for 0.4 to 24 yr were treated with pyridoxine-ATP infusion for approx 12 to 30 days. In patients with no evidence of hepatoma, increased serum AFP levels diminished gradually following treatment. In patients with definite hepatoma the serum AFP levels increased. None of the hepatoma patients responded to the treatment. These results may offer a new approach to the earlier detection of primary hepatomas in these patients. (15 Refs)

32. SISTER-CHROMATID EXCHANGES BEFORE AND AFTER HAIR DYEING.

Kirkland DJ, Honeycombe JR, Lawler SD, Venitt S, Crofton-Sleigh C

Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire HR8 1LG, England

Mutat Res; 90(3):279-286 1981

Cytogenetic changes were evaluated in peripheral lymphocytes of 14 volunteers (13 women and 1 man) after a single application of hair dye. Six hr after dyeing, six volunteers showed increases and eight showed decreases in mean number of sister-chromatid exchanges (SCE). No statistically significant differences were observed in mean SCE/cell between predyeing samples and those taken at 6 hr or 7 days after dyeing. (15 Refs)

33. COMPARISON OF VARIOUS PROMOTING AGENTS ON THE INDUCTION OF PRENEOPLASTIC LESIONS IN THE RAT LIVER (MEETING ABSTRACT).

Ito N, Tsuda H, Hasegawa R, Imaida K

Nagoya City University Medical School, Nagoya 467, Japan

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Rats were injected ip with N-nitrosodiethylamine (DEN) or saline (control) as an initiator. Two wk after this, rats were given test compounds mixed in the basal diet or drinking water for six wk and then killed. The results show that administration of strong hepatocarcinogens such as aflatoxin B1, DEN, N-nitrosodimethylamine (DMN), 2-acetylaminofluorene (2-AAF), 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), thioacetamide, sterigmatocystin and ethionine resulted in large numbers of hyperplastic (neoplastic) liver nodules, whereas, dieldrin, dichloro-diphenyl trichloroethane (DDT), polychlorinated biphenyls, and alpha-hexachlorocyclohexane had less promoting effects. Non-hepatocarcinogens, such as N-nitrosoethylurea and 3-methylcholanthrene, also slightly enhanced the induction of hyperplastic nodules. Of the miscellaneous compounds tested, phenobarbital, deoxycholic acid and ethinyl estradiol enhanced the nodule induction. Hepatocarcinogens and chemicals with promoting activity in liver carcinogenesis gave positive results in this system. Thus our system could be used for screening hepatocarcinogens or hepatopromoters and also estimating their potency. (no Refs)

HETEROCYCLIC AMINES

34. PROMOTING EFFECT OF TESTOSTERONE PROPRIONATE ON EXPERIMENTAL EXOCRINE PANCREATIC TUMORS BY 4-HYDROXYAMINOQUINOLINE 1-OXIDE IN RATS.

Hayashi Y, Katayama H

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Toxicol Lett; 9(4):349-354 1981

The promotion of 4-hydroxyaminoquinoline 1-oxide (HAQO) induced pancreatic tumors by androgenic hormone was tested in male and female rats. Three male (1m, 2m, and 3m) and three female groups (1f, 2f, and 3f) each consisting of 20 rats received 9 mg/kg iv injection of HAQO. Groups 1m and 1f received no further treatment. All other groups were castrated and subsequently given weekly sc injections of 1 mg testosterone propionate (groups 3m and 3f) or 0.1 ml olive oil (groups 2m and 2f). At 400 days the rats were autopsied and representative samples of pancreatic tumors were examined by electron microscopy. Eight exocrine adenomas of the pancreas developed in group 1m; six exocrine tumors developed in group 3m. One exocrine insuloma pancreatic tumor developed in group 1f and five were observed in group 3f. No exocrine adenomas of the pancreas developed in the control group or in groups 2m or 2f. Apparently testosterone can promote the induction of pancreatic tumors in rats by HAQO. (9 Refs)

35. EFFECT OF CAFFEINE (CF) ON PANCREATIC CARCINOGENESIS OF 4-HYDROXYAMINO-QUINOLINE 1-OXIDE (4-HAQO) IN RATS (MEETING ABSTRACT).

Konishi Y, Denda A, Yokose Y, Takahashi S

Department of Oncological Pathology, Cancer Center, Nara Medical College, Kashihara, Nara 634, Japan

Newsletter Natl Pancreas Cancer Project; VI(2):31 1981

Sixty male Wistar rats weighing 160 g were used. 4-HAQO, at a dose of 7 mg/kg was given by iv injection and CF was given by sc injection for 12 hr intervals. Group (G) 1 received 4-HAQO at 3 days after partial pancreatectomy (PP) G 2 received 6 x injections of 120 mg/kg of CF before 4-HAQO which was given 3 days after PPGs 3, 4, and 5 received 12 x injections of 120, 60, and 30 mg/kg of CF after 4-HAQO which was given 3 days after PP, respectively. All rats were sacrificed at 52 wk, and examined macroscopically and histologically. The numbers of pancreatic tumors counted macroscopically were 14.9 +/-6.6 in G 1, 10.0 +/-5.9 in G 2, 6.0 +/- in 3.2 G 3, 22.7 +/-8.3 in G 4, and 28.1 +/-11.4 in G 5. These results suggest that CF showed biphasic effects, inhibitory and enhancing ones, on the pancreatic carcinogenesis of 4-HAQO in rats. (no Refs)

36. MORPHOLOGIC ANALYSIS OF ATYPICAL ACINAR CELL LESIONS (AACL) INDUCED IN RAT PANCREAS BY 4-HYDROXYAMINOQUINOLINE-1-OXIDE (4-HAQO) (MEETING ABSTRACT).

Rao MS, Upton MP, Subbaroa V, Scarpelli DG

Department of Pathology and Cancer Center, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL, 60611

Newsletter Natl Pancreas Cancer Project; VI(2):48 1981

A metabolite and possible proximate carcinogen of 4-nitroquinoline-1-oxide, 4-HAQO, is both toxic and carcinogenic for pancreas. A single IV injection of 4-HAQO in male Wistar rats at a dose of 6 mg/kg body wt induced AACL in 100% of the animals. AACL could be classified histologically as zymogen-poor and zymogen-rich foci, and zymogen-rich nodules (grossly visible). The zymogen-poor foci contained between 20-300 cells and rarely more than 500 cells. Cells in such foci were large, contained a large irregular nucleus with a prominent nucleolus, and a markedly basophilic cytoplasm with a few to small numbers of zymogen granules. By transmission electron microscopy (TEM) these cells showed markedly irregular lateral plasma membranes, a well developed rough endoplasmic reticulum (RER) and a few zymogen granules. Cells in zymogen-rich foci and nodules were arranged in acini which were larger than adjacent acini. The cells contained an intensely eosinophilic granular cytoplasm, and a large oval basophilic nucleus with a prominent nucleolus. By TEM, the cells showed a zymogen rich cytoplasm, RER and irregular lateral membranes. The mitotic and [3H] thymidine labeling indices respectively of both cell variants of AACL were as follows: eosinophilic cells, 2.75 and 23.2 basophilic cells 0.125 and 1.2 as compared to 0 and 1 for normal pancreatic acinar cells. These studies indicate that 4-HAQO induces at least 2 varients of AACL with different morphological features and growth potential. Their role in the pathogenesis of acinar cell adenomas and carcinomas remains to be elucidated. (no Refs)

37. QUANTITATIVE MUTAGENESIS AND MUTAGEN SCREENING WITH MAMMALIAN CELLS: TOWARD A COMPREHENSIVE CHINESE HAMSTER GENETIC TOXICITY SYSTEM (MEETING ABSTRACT).

Hsie AW

Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830

Toxicologist; 1(1):40 1981

We have employed Chinese hamster ovary (CHO) cells to develop and define a mutational assay at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus. Coupled with S9 metabolic activation system, the CHO/HGPRT assay permits quantification of gene mutation and cytotoxicity induced by various classes of mutagens including 3 aklanesulfonates, 2 alkylsulfates, 3 nitrosoguanidines, 3 nitrosoureas, 19 heterocyclic mustards (ICR compounds), 6 platinum(II)chloroammines, 7 quinolines, 8 nitrosamines, 3 haloethanes, 4 polyaromatic hydrocarbons. Such study elucidates the structure-activity relationship for a given class of direct-acting mutagens. All carcinogens investigated, except ICR 191, showed mutagenic activity; and all noncarcinogens were nonmutagenic. The CHO/HGPRT system can also simultaneously measure mutagen-induced chromosome aberration and sister chromatid exchange (SCE) which led to the development of the Multiplex CHO Genetic Toxicity Assay. Recent studies have shown that it is feasible to determine chromosomal deletion and loss using a CHO/human hybrid cell line and to develop a Chinese hamster system for studies of induction of mutation at the HGPRT locus, chromosome aberration and SCE of peripheral blood lymphocytes. The use of such a comprehensive Chinese Hamster Genetic Toxicity System consisting of these four assays at the cellular and organismic level should enable a sensitive and reliable identification of suspected environmental mutagens. (no Refs)

38. EVIDENCE SUGGESTING THAT THE MECHANISM FOR AEROBIC AND HYPOXIC CYTOTOXICITY OF NITROHETEROCYCLES IS THE SAME (MEETING ABSTRACT).

Oliver PL

The Johns Hopkins Oncology Center, Baltimore, MD, 21205

Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17 -20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

The preferential sensitivity of hypoxic cells to nitroheterocycles is generally thought to be due to toxic products formed only under hypoxia. However, under air, reaction of highly unstable intermediates with oxygen results in production of superoxide and hydrogen peroxide, both of which are toxic. Despite the suggestion that aerobic and hypoxic toxicity may be due to these different species, the relation between redox potential and cytotoxicity is similar for both aerobic and hypoxic cell killing. The only species formed under both situations (and at the same rate) is the nitro anion radical. It thus seems likely that this intermediate is solely responsible for the toxicity of nitro compounds, and that cells are more sensitive under hypoxia because the nitro radical has a longer half-life in the absence of oxygen. Our studies on cellular accumulation of fluorescent nitroheterocycles (4-Nitroquinoline-1-oxide, 4-NQO; furylfuramide, AF-2; Squibb 18,506) show that toxicity can be correlated with the amount of nitro compound bound intracellularly. This correlation is independent of oxygen concentration; at equitoxic concentrations, an equal amount of drug is bound under either aerobic or hypoxic conditions. Increased drug uptake under hypoxia results when complete drug reduction creates a sink for the influx of more drug. These results predict that chemical species which interfere with auto-oxidation of the anion radical or compete for oxygen should increase aerobic toxicity of nitroheterocycles. Conversely, sulfhydryl agents, which bind these radicals, should protect equally well under aerobic or hypoxic conditions. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

39. ADVANCES IN THE METABOLIC ACTIVATION OF CARCINOGENS.

Ivanetich KM
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, South Africa
S Afr Cancer Bull; 25(1/2):105-116 1981

Of the known chemical carcinogens, an ever-increasing number require metabolic activation to elicit their mutagenic and carcinogenic effects. In a review, it is noted that the enzymes known as cytochrome P-450 alone or in conjunction with other enzymes are involved in this activation. The activated metabolites may initiate carcinogenesis by covalently binding to selected sites on nuclear DNA in somatic cells. Detailed pathways are presented for a number of carcinogens, such as chlorinated ethylenes, aflatoxin B1, acetylaminofluorene and benzpyrene. (22 Refs)

40. PROMOTION IN URINARY BLADDER CARCINOGENESIS (MEETING ABSTRACT).

Cohen SM
University of Nebraska College of Medicine, Omaha, NE
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Aromatic amines, including, 2-naphthylamine, 4-aminobiphenyl, and benzidine, are known urinary bladder carcinogens in man and other species, but in rodents, aromatic amines and amides have usually induced liver tumors, occasionally also with tumors of the bladder and other tissues. Variations in organ spicificity are related to differences in metabolism; for bladder the rates of acetylation and deacetylation appear to be critical. Bladder specific carcinogens in rodents and other species have subsequently been identified, including N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) administered in the drinking water, N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT) in the diet and N-methyl-N-nitrosourea (MNU) instilled intravesically. When low doses of several baldder carcinogens (BBN, FANFT, 2-acetylaminofluorene, and 3,3'-dichlorobenzidine) are administered to rats, either simultaneously or sequentially, a synergistic effect is observed with respect to bladder carcinogenesis. In addition, multistage carcinogenesis has been demonstrated in rats for the bladder using MNU or FANFT as initiators, and sodium saccharin, sodium cyclamate, or tryptophan in the diet as promoters. The urothelium normally has a very low mitotic rate. If mucosal proliferation is increased, such as during fetal development or during regeneration and repair of an ulcer, the bladder appears to be considerably more sensitive to the effects of promoting substances. For example, if sodium saccharin is administered to rats after ulceration of the bladder, even without prior administration of an initiator, bladder carcinoma develops. Under these conditions, the substance appears as a carcinogen. Human populations with increased bladder epithelial proliferation, such as the fetus, infants, patients with bacterial cystitis, or men with partially obstructive prostatism, may have increased susceptibility to the action of carcinogenic or promoting stimuli. (no Refs)

41. CARCINOMA OF THE BLADDER.

Tauber R
Urol. Univ.-Klinik, Klinikum Grosshadern, Marchioninistrasse 15, 8000 Munchen 70, W. Germany
Fortschr Med; 99(40):1630-1636 1981

The occurrence, diagnosis, and treatment of bladder cancer is reviewed. The etiology of such tumors is discussed with regard to the role of carcinogens, such as aromatic amines, and the increased risk of bladder cancer associated with specific occupations, such as those of painters and textile workers. The classification of bladder tumors is described with respect to histological criteria established by the World Health Organization, clinical TNM (tumor, node, metastases) staging and histopathologic P-classification, and various growth forms of the tumors. Symptoms of bladder tumors are outlined, and the value of different diagnostic procedures in correctly assessing TNM stages is considered. Surgical treatment of bladder tumors is discussed; emphasis is placed on factors which influence the choice of the initial surgical procedure and of the procedure to be used with recurrent tumors. Methods, indications, and advantages are described for transurethral resection, partial bladder resection, cystectomy, and urinary diversion following cystectomy. The efficacy of chemotherapy and radiotherapy in the treatment of these tumors is considered. The prognoses for patients with bladder tumors are examined; it is noted that early detection and accurate diagnosis have positive effects on prognosis. (no Refs) (In GER)

42. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA
Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205
Epidemiol Rev; 3:203-229 1981

Well-known risk factors for bladder cancer are reviewed briefly; unresolved aspects of bladder cancer epidemiology are explored. Topics include mortality and incidence rates (international comparisons, demographic and geographic characteristics, time trends, personal characteristics), latency, cell type, and risk factors (smoking, sugar substitutes, coffee drinking, occupations, hair dyes, Schistosoma haematobium, risks in case clusters, viruses, drug use, and other factors and diseases). Published data on age-adjusted death rates for malignant neoplasms of bladder and other urinary organs for selected countries, annual incidence rates for selected cancer registries, age-specific death rates for malignant neoplasms of urinary organs by race and sex, correlation of age-adjusted death rates for malignant neoplasms of bladder and other urinary organs by sex for states, age-adjusted mortality and incidence rates for bladder cancer by sex for white and nonwhite races, association of smoking, coffee consumption, specific chemicals from the dye industry, and occupations with bladder cancer, and descriptive characteristics of studies relating occupation with risk of bladder cancer are presented. (108 Refs)

43. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.

Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

A review is presented of incidence, risk factors, and chemical and environmental agents involved in induction or promotion of cancer of the gastrointestinal system. Presence of ingested agents in foods and experimental and clinical evidence for cancer causation are discussed. Carcinogenesis is considered with respect to the esophagus (nitrosamines, mycotoxins, promotional factors), stomach (nitrites and polycyclic hydrocarbons, mycotoxins, agricultural products, polychlorinated biphenyls, experimental carcinogens), and large bowel (nitrites, aflatoxins, diet, carrageenan, chemical carcinogens: nitroso compounds, biphenyls, symmetrical 1,2-dialkylhydrazines and azoalkanes and azoxyalkanes). Chemicals with known gastric tumor induction capability in animals are tabulated from published reports. (74 Refs)

44. PROPORTIONATE MORTALITY STUDY OF FUR DYERS (MEETING ABSTRACT).

Haring MK, Waxweiler RJ, Walrath J
National Institute for Occupational Safety and Health, Cincinnati, OH
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

In recent studies, numerous constituents of oxidative hair dyes were shown to be mutagenic by the Ames test; some were also proven to be carcinogenic, inducing tumors of the liver, lymphatic system or other sites, in laboratory animals. Epidemiologic studies have associated exposure to hair dyes with increased risks of breast, cervical and lung cancers and chromosomal damage among hairdressers and consumers. During the past century, fur dyers have used oxidative dyes extensively to tint and color animal fur. To investigate the health effects of long term exposures to oxidative dyes, a retrospective cohort mortality study is being conducted on 980 fur dyers and processors of the Fur, Leather and Machinists Workers Union who were pensioned between 1952 and 1977. The standardized mortality ratio (SMR), using age-sex-race, calendar time, and cause-specific mortality rates for United States, will be calculated for all causes of death including all malignant neoplasms. In addition to oxidative dyes, other possible occupational exposures are saw dust, used to absorb excess dye from furs, and formaldehyde. Analyses of job classifications and ethnic origins also will be conducted. (no Refs)

45. PATTY'S INDUSTRIAL HYGIENE AND TOXICOLOGY. VOLUME 2A. TOXICOLOGY.

Clayton GD, Clayton FE

San Luis Rey, CA

Patty's Industrial Hygiene and Toxicology. Volume 2A. Toxicology. New York, John Wiley and Sons, 1467-2878 pp., 1981.

Toxicity and other data are presented for elements and compounds that are currently of primary interest to industry. Individual chapters describe the sources and production, uses and industrial exposures, physical and chemical properties, acute and chronic toxicity, carcinogenicity, and mutagenicity of 40 metals, organic sulfur compounds, epoxy compounds, esters, ethers, aromatic nitro and amino compounds, phenols and phenolic compounds, aldehydes and acetals, heterocyclic and miscellaneous nitrogen compounds, and phosphorus, selenium, and tellurium. Analytic procedures and recommended threshold limit values also are discussed. (4197 Refs)

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DIETARY FACTORS IN CARCINOGENESIS

1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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CHEMICAL CARCINOGENESIS

Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/05

MAY, 1982

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ANILINES AND EXTENDED ANILINES

1. SISTER CHROMATID EXCHANGE INDUCTION AND CELL CYCLE INHIBITION BY ANILINE AND ITS METABOLITES IN HUMAN FIBROBLASTS.

Wilmer JL, Kligerman AD, Erexson GL
Dept. Genetic Toxicology, Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709

Environ Mutagen; 3(6):627-638 1981

The effects of aniline HCL, para-aminophenol (pAP), ortho-aminophenol (oAP), acetanilide (AA), para-hydroxy-acetanilide (pOHAA), ortho-hydroxyacetanilide (oOHAA), and N-phenylhydroxylamine (PHA) on sister chromatid exchange (SCE) and cell proliferation were investigated in human fibroblasts. Although considerable diversity in cytological effects was observed, oAP and PHA were the only compounds found to induce dose-dependent increases in SCE. With 0.1 milliM (mM) oAP the SCE frequency was doubled; at 0.1 mM PHA the SCE frequency was increased 40% over controls. PHA appeared to inhibit cell proliferation to a greater extent than oAP. A slowing of the cell cycle was observed with 0.01 mM PHA and with 0.1 mM oAP. Concentrations of 0.5 mM PHA

HE 20. 3173/2:

and 0.3 mM oAP caused extensive cell death. Aniline HCL induced minimal but significant increases in SCE. On the basis of SCE frequency per millimole, oAP was approx 3.1x more potent than PHA; PHA was approx 87.4x more potent than aniline HCl. pOHAA (10 mM) induced pronounced inhibition of cell replication but no increases in SCE. Determination of mitotic indices proved to be far less sensitive as an indicator of toxicity than cell cycle analysis. (56 Refs)

2. STUDIES ON THE TOXICITY OF CHLORINATED P-NITROBIPHENYL ETHER. I - METHEMOGLOBIN FORMATION IN VITRO AND IN VIVO INDUCED BY NITROSO AND AMINO DERIVATIVES OF CHLORINATED BIPHENYL ETHER.

Miyauchi M, Koizumi M, Uematsu T
(c/o Uematsu) Dept. Chemical Hygiene, Hokkaido Inst. Pharmaceutical Sciences, Otaru 047-02, Japan
Biochem Pharmacol; 30(24):3341-3346 1981

Methemoglobin (Mg) formation by nitroso and amino derivatives of chlorinated biphenyl ether was investigated. The nitroso derivatives used induced Mg formation in suspensions of human RBC. Ability to induce Mg formation among the nitroso derivatives was the highest for nitrosobenzene, followed by p-nitrosobiphenyl ether, 4-chloro p-nitrosobiphenyl ether, 2,4-dichloro p-nitrosobiphenyl ether and then 2,4,6-trichloro p-nitrosobiphenyl ether. Therefore, the ability to induce Mg formation depended on the number of chlorines rather than on the position of chlorine substitution on the phenoxy group in the molecule. Since lactate decreased but glucose and xylitol increased the Mg level produced by the nitroso compounds, this reaction would appear to require an NADPH-dependent enzyme system in RBC. The amino derivatives used induced Mg formation in suspensions of human RBC with rat liver homogenates. Ability to induce methemoglobin formation among the amino derivatives was the highest for p-aminobiphenyl ether, followed by 4-chloro p-aminobiphenyl ether, 2,4-dichloro p-aminobiphenyl ether, 2,4,6-trichloro p-aminobiphenyl ether, and then aniline. After ip injection, methemoglobinemia was induced by p-aminobiphenyl ether, aniline, and 2,4-dichloro p-aminobiphenyl ether but not by 2,4,6-trichloro p-aminobiphenyl ether over the period tested. The order of Mg formation was p-aminobiphenyl ether greater than or equal to 4-chloro p-aminobiphenyl ether greater than aniline greater than or equal to 2,4-dichloro p-aminobiphenyl ether. Oral administration gave almost the same result as ip injection. The max Mg levels produced by the amino derivatives were highest for 4-chloro p-aminobiphenyl ether, followed by p-aminobiphenyl ether, 2,4-dichloro p-aminobiphenyl ether, aniline, and then 2,4,6-trichloro p-aminobiphenyl ether. However, the Mg level produced by 2,4,6-trichloro p-aminobiphenyl ether was very low and not significantly greater than the background level. (Author abstract) (35 Refs)

FLUORENAMINES: IN VIVO

3. NEUTRAL GLYCOSPHINGOLIPIDS OF RAT LIVER AND HEPATOMAS: COMPOSITION, BIOSYNTHESIS AND ALTERATIONS IN TUMORIGENESIS.

Walter VP
Purdue University, Lafayette, IN, 47907
Diss Abstr Int [B]; 42(5):1725-B 1981

Neutral glycosphingolipids (NGSL) undergo alterations as one result of the tumorigenic process. The purpose of this study was to examine these alterations in transplanted hepatoma lines and to determine if selective enzymatic synthesis was responsible. NGSL were extracted and purified from transplanted hepatomas, from sera of tumor-bearing rats, and from livers of rats fed the carcinogen 2-acetylaminofluorene and compared to livers and sera of control animals. To quantitate NGSL at the cell surface, a method of plasma membrane isolation from transplanted hepatomas was adapted. Lastly, the biosynthesis of ceramide, glucosylceramide, and lactosylceramide were examined in these same tissues. (no Refs)

FLUORENAMINES: IN VITRO

4. REPAIR OF ETHYLNITROSOUREA-INDUCED DNA DAMAGE IN THE NEWBORN RAT. II. LOCALIZATION OF UNSCHEDULED DNA SYNTHESIS IN THE DEVELOPING RAT BRAIN.

Heyting C, Van't Veer L
Div. Chemical Carcinogenesis, Antoni van Leeuwenhoekhuis, The Netherlands Cancer Inst., 121, Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Carcinogenesis; 2(11):1173-1180 1981

The developing rat brain is extremely sensitive to tumor induction by N-ethyl-N-nitrosourea (ENU). This sensitivity is ascribed to a defective repair of ENU-induced DNA damage. Because the different cell types of the developing rat brain are heterogeneous in their sensitivity to tumor induction, we decided to localize DNA-repair activities within this organ. In this paper we describe the localization of carcinogen-induced unscheduled DNA synthesis (UDS). Fresh brain slices were incubated in medium containing carcinogen and [3H]thymidine, and the incorporation of tritium was detected by autoradiography. We used two carcinogens, namely ENU (a short-patch repair agent) and the long-patch repair agent N-acetoxy-N-acetyl-2-aminofluorene (AAAF). Both carcinogens induced UDS in all nuclei in brains from 1-day-old rats. In brains from 10-day-old rats all neurons except the maturing granule cells of the cerebellum and the dentate gyrus had lost their capacity for ENU-induced UDS. In brains from 26-day-old rats no more neurons carried out ENU-induced UDS. The results obtained with AAAF resemble those obtained with ENU. However, neurons tend to lose their capacity for ENU-induced UDS earlier than that for AAAF-induced UDS: in brains from 10-day-ol d rats some of the neurons of the cerebral cortex and the thalamus were still capable of carrying out AAAF-induced UDS; in brains from 26-day-old rats AAAF-induced UDS could still be detected in some of the neurons of the thalamus. Those cells that are supposed to be sensitive to tumor induction by chemical carcinogens are still capable of carrying out ENU- as well as AAAF-induced UDS. Thus, the susceptibility of the different types of rat brain cells to tumor induction does not correlate with an inability to carry out carcinogen-induced UDS. (Author abstract) (33 Refs)

5. ENHANCEMENT OF S9 ACTIVATION BY S105 CYTOSOLIC FRACTION.

Forster R, Green MH, Priestley A
Water Res. Center, Henley Road, Medmenham, Marlow, Buckinghamshire, England
Carcinogenesis; 2(11):1081-1085 1981

The addition of supplementary cytosolic fraction greatly enhances the activation of 2-acetylaminofluorene (AAF) by uninduced 9,000 x g supernatant fraction (S9) in the Ames test. Uninduced S9 is poor at activating AAF in the Ames test (although it is effective in the liquid based fluctuation test) probably because cytosolic material diffuses into the bottom agar. An enhancing effect of cytosol supplementation was also observed with 2-aminoanthracene (AA) and 2-aminofluorene (AF) with uninduced S9. Using Aroclor-induced preparations, supplementation with cytosol enhanced the activation of benzo[a]pyrene and ethidium bromide. With AAF and Aroclor-induced preparations, supplementation with cytosol produces a slight but significant increase in activation, but interpretation is complicated by the fact that Aroclor 105,000 x g supernatant fraction (S105) alone efficiently activates AAF, AF and AA. Norharman potentiated the enhancing effect of Aroclor S105 on Aroclor-S9 activation of AAF but inhibited the activation of AAF by S105 fraction alone. The enhancing effect of S105 fraction may explain some, but not all, of the differences between liquid-based and agar overlay based activation. (Author abstract) (26 Refs)

6. GENETIC EVIDENCE FOR MANY UNIQUE LIVER MICROSOMAL P-450-MEDIATED MONOOXYGENASE ACTIVITIES IN HETEROGENEIC STOCK MICE.

Lang MA, Gielen JE, Nebert DW

Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205

J Biol Chem; 256(23):12068-12075 1981

Total cytochrome P-450 content, the Soret maximum of the reduced P-450-CO complex, NADPH-cytochrome c reductase activity, and 20 monooxygenase activities were determined in liver microsomes from each of 12 individual Heterogeneic Stock (HS) mice at varying times after 3-methylcholanthrene treatment. The choice of genetically very heterogeneous mice and the possibility of different turnover rates (synthesis/degradation) during the 3-methylcholanthrene induction process provided us with a strong like lihood of detecting differences in drug-metabolizing enzyme activities. Such diversity would also be expected among the human population. The substrates included benzo[a]pyrene, ethoxyresorufin, biphenyl, p-nitroanisole, 2-acetylaminofluorene, 7-ethoxycoumarin, zoxazolamine, estradiol-17beta, testosterone, progesterone, pregnenolone, dehydroepiandrosterone, and aldrin. By two-factor analysis of variance, 18 unique liver microsomal monooxygenase activities appear to be distinctly different from one another, out of the 20 activities chosen for study. Ethoxyresorufin O-deethylase activity is significantly correlated ($p = 0.11$) with aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity. Dehydroepiandrosterone 16alpha-hydroxylase activity correlates well with the testosterone ($p = 0.33$), progesterone ($p = 0.16$), and pregnenolone ($p = 0.11$) 16alpha-hydroxylases. Testosterone 16alpha-hydroxylase, progesterone 16alpha-hydroxylase, and pregnenolone 16alpha-hydroxylase activities, on the other hand, are all significantly (p less than 0.001) different from one another. These data with intact microsomes illustrate the complexity of the problem with multiple P-450-mediated monooxygenases. Almost every activity therefore appears to be unique and probably reflects the aggregate contribution from numerous forms of P-450. (Author abstract) (33 Refs)

7. STRUCTURAL GENE PRODUCTS OF THE AH LOCUS. EVIDENCE FOR MANY UNIQUE P-450-MEDIATED MONOOXYGENASE ACTIVITIES RECONSTITUTED FROM 3-METHYLCHOLANTHRENE-TREATED C57BL/6N MOUSE LIVER MICROSOMES.

Lang MA, Nebert DW

Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205

J Biol Chem; 256(23):12058-12067 1981

Cytochrome P-450 from cholate-solubilized liver microsomes prepared from 3-methylcholanthrene-treated genetically 'responsive' C57BL/6N mice (Ahb/Ahb) was partially purified by aminooctyl-Sepharose 4B column chromatography with an elution buffer that included Emulgen 911, followed by hydroxylapatite column chromatography. The P-450 was separated into 16 fractions: 15 fractions principally associated with the Ahb allele and induction by 3-methylcholanthrene and 1 fraction not associated with the Ahb allele, ie predominantly constitutive form(s) of P-450. The metabolism of benzo[a]pyrene, 7-ethoxycoumarin, biphenyl, ethoxyresorufin, acetanilide, 2-acetylaminofluorene, phenacetin, estradiol-17beta, and testosterone was investigated. With these nine substrates, we examined the rates of formation of 17 products, ie 17 P-450-mediated reconstituted monooxygenase 'activities,' in each of the 16 fractions. Differing reductase/cytochrome and lipid/cytochrome requirements were observed for each activity; the reasons for these empirical differences are not known. By two-factor analysis of variance, our data for 17 catalytic activities can be explained by a minimum of 19 unique groups of monooxygenase activities: 12 induced by 3-methylcholanthrene and 7 control (endogenous). At least one of these distinctly different 3-methylcholanthrene-induced groups and at least one of these constitutive groups is associated with a marked blue spectral shift (approx 2.0 nm) in the Soret peak of the reduced hemoprotein-CO complex, suggesting multiple forms of inducible and control 'P-448.' Almost every reconstituted monooxygenase activity therefore appears to be unique and probably represents the aggregate activity from numerous forms of P-450. (Author abstract) (43 Refs)

OTHER FUSED RING AMINES

8. INHIBITION OF VIRUS TRANSFORMATION BY HIGH ENERGY FUELS AS A CORRELATE OF CARCINOGENIC POTENTIAL.

Blakeslee JR
Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH
Sci Tech Aerosp Rep; 19(18):2533 1981

Hydrazine and naphthylamines and their derivatives were assayed for co-carcinogenic effects on ST FeSV-directed transformation of human cells. All chemicals tested at non-toxic concentrations showed anti-carcinogenic activity. The temporal relationship of chemical treatment to virus infection was more critical with the hydrazines than with the naphthylamines in that max anti-carcinogenic effect occurred when virus-infected cells were exposed to the hydrazines 2 hr post-infection, whereas the naphthylamines anti-carcinogenic effect was observed if cells were exposed either pre- or post-infection. The anti-carcinogenic effect, when compared with in vitro chemical transformation and neoplastic transformation, show a high degree of correlation. These data suggest this assay system may lend itself to a rapid screen (9-13 days) of chemicals for carcinogenic potential. Cytotoxic results showed no significant difference in shale oil or petroleum derived JP5 or DFM. (Author abstract) (no Refs)

9. PULMONARY ADENOMA RESPONSE OF STRAIN A MICE TO SULFONIC ACID DERIVATIVES OF 1-AND 2-NAPHTHYLAMINES.

Theiss JC, Shimkin MB, Weisburger EK
Univ. Texas Health Science Center at Houston, Sch. Public Health, P.O. Box 20186, Houston, TX, 92093
JNCI; 67(6):1299-1302 1981

Various sulfonic acid derivatives of 1-naphthylamine and 2-naphthylamine were tested in inbred A/St (male and female) mice by the pulmonary adenoma bioassay to determine if this class of compounds, used as intermediates in the dye-stuff industry, possesses tumorigenic activity. neither 1-naphthylamine nor the four sulfonic acid derivatives of 1-naphthylamine tested were tumorigenic. However, 2-naphthylamine and two of the three sulfonic acid derivatives of 2-naphthylamine tested produced statistically significant lung tumor responses at comparable doses. These results indicated that this class of compounds should be examined more extensively for carcinogenic activity. (Author abstract) (25 Refs)

10. A CHROMATOGRAPHIC TECHNIQUE FOR THE ANALYSIS OF OXIDIZED METABOLITES: APPLICATION TO CARCINOGENIC N-HYDROXYARYLAMINES IN URINE.

Frederick CB, Mays JB, Kadlubar FF
Div. Carcinogenesis Res., Natl. Center Toxicological Res., Dept. Health and Human Services, Jefferson, AK, 72079
Anal Biochem; 118(1):120-125 1981

A new chromatographic detection method for oxidized metabolites has been developed based on the reaction of eluted compounds with an Fe+++-bathophenanthroline colorimetric reagent in a postcolumn reactor. The method is sensitive to N-hydroxyarylamines, aryldiamines, phenolic amines, and ascorbic acid. It has been applied to the analysis of toxic N-oxidized metabolites in rhesus monkey urine after the animals were dosed with the bladder carcinogens, 1-and 2-napthylamine. These compounds are oxidized to the corresponding N-hydroxyarylamines in the liver, conjugated at the N-glucuronide, and excreted in the urine. The N-glucuronide has been shown to undergo acidic hydrolysis in the urine to release the free N-hydroxyarylamine, an ultimate carcinogen for the induction of bladder tumors. In this study, the N-hydroxy-N-glucuronide of 2-naphthylamine was found to be excreted at the rate that was 6.8x that of the 1-naphthylamine isomer. This is consistent with the much higher carcinogenic potency of 2-naphthylamine in a variety of species. (Author abstract) (18 Refs)

11. LACK OF COMUTAGENICITY BY NORHARMAN AND OTHER COMPOUNDS ON REVERTANTS INDUCED BY PHOTOLABELING WITH 2-AZIDO-9-FLUORENONE OXIME.

White WE, Rock SG
Div. Molecular Biology, Univ. Alabama, Birmingham, AL, 35294
Mutat Res; 84(2):263-271 1981

Effects of several comutagenic or cocarcinogenic compounds on photolabel-induced mutagenesis were examined. Photolabeling with 2-azido-9-fluorenone oxime was used to produce mutagenic adducts directly, thereby bypassing metabolic requirements for aromatic amines. DNA-binding compounds ethidium, harman, and norharman at concentrations as low as 10(-6) M slightly reduced photolabel-induced mutagenesis in Salmonella typhimurium strain TA1538. Retinol (10(-6) to 10(-4) M) had no effect on mutagenesis or on toxicity. Cholic acid had no effect at concentrations less than 10(-5) M but decreased mutagenicity at 10(-4) M. Decreases in mutation rates could be a result of competition for binding sites, resulting in formation of fewer critical adducts. If this is true, binding of particular agents to DNA could be antimutagenic for some mutagens and comutagenic for mutagens with adducts at different positions. (22 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

12. HIGHLY-PERMEABLE INTERCELLULAR COMMUNICATIONS AND ELECTRICAL CHARACTERISTICS OF NORMAL LIVER AND HEPATOMA. I. HIGHLY-PERMEABLE INTERCELLULAR COMMUNICATIONS IN INDUCED MURINE HEPATOMA.

Sharovskaia IuIu, Mittel'man LA, Smolianinov VV, Chailakhian LM
Res. Lab. Molecular Biology and Bio-organic Chemistry, M. V. Lomonosov State Univ., Moscow, USSR
Tsitologiia; 23(10):1142-1148 1981

Permeability of the intercellular communications was studied in C3HA mice with o-aminoazotoluene-induced hepatomas. Transmembrane potentials, the input resistance, and distribution of the electric potential measured in hepatoma tissue at different stages of carcinogenesis did not differ from those in normal liver tissue. It was suggested that highly-permeable intercellular communications play a nonspecific role in malignant transformation. (12 Refs) (In RUS)

13. MUTAGENICITY OF URINARY METABOLITES OF BENZIDINE AND BENZIDINE-BASED AZO DYES.

Tanaka K, Mii T, Marui S, Matsubara I, Igaki H
Toray Shiga Hosp., 2-7-35 Sonoyama, Otsu, 520, Japan
Int Arch Occup Environ Health; 49(2):177-185 1981

Mutagenicity of urinary metabolites of benzidine and benzidine-based azo dyes was studied. Mutagenicity of the urine extracts was tested in the Salmonella/mammalian-microsome assay. Results of the mutagenicity assay and gas chromatography analysis of the urine extracts suggested that the azo dyes may decompose and release benzidine. The urinary metabolites of benzidine were more mutagenic than benzidine itself. Azo dyes studied were Direct Deep Black EX and Congo Red, both containing a 4,4'-diazobiphenyl group. (23 Refs)

14. DOSE RESPONSES OF FIVE HEPATOCARCINOGENS FOR THE INITIATION OF RAT HEPATOCARCINOGENESIS.

Imaida K, Shirai T, Tatematsu M, Takano T, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuhc-cho, Mizuho-ku, Nagoya 467, Japan
Cancer Lett; 14(3):279-283 1981

Dose response curves were generated for hepatocarcinogenesis in male Fischer 344 rats initiated by diethylnitrosamine (DEN), aflatoxin-B1 (AFB), N-2-fluorenylacetamide (FAA), 3'-methyl-4-dimethylaminobenzene (DAB), or dimethylnitrosamine (DMN). Two wk after initiation, animals were placed on a 0.02% FAA diet for 2 wk. Animals were partially hepatectomized (PH) at the end of wk 3 and killed at the end of wk 4. All five hepatocarcinogens exhibited clear dose response curves for initiation of hepatocarcinogenesis; both numbers and areas of hyperplastic nodules increased with increasing doses in all cases. AFB was the most potent initiator, and was effective at a dose as low as 0.25 mg/kg body wt. Sizes of nodules induced by DEN, FAA, and DMN were smaller than those induced by AFB and DAB. (12 Refs)

15. LACK OF CARCINOGENICITY IN MICE OF 4,4'-DIAMINOBENZANILIDE AND 4,4'-DIAMINOAZOBENZENE, TWO INTERMEDIATES USED IN THE MANUFACTURE OF AZO DYES.

Della Porta G, Dragani TA
Via G. Venezian 1, Instituto Nazionale Tumori, 20133 Milano, Italy
Cancer Lett; 14(3):329-336 1981

A long-term bioassay for carcinogenicity of 4,4'-diaminobenzanilide (DABA) and 4 ,4'-diaminoazobenzene (DAAB) was conducted in BALB/c mice. Male and female mice received DABA or DAAB in the diet (100, 300, or 600 ppm) beginning at 8 wk of age and continuing for 60 wk. Animals were then returned to a normal diet and observed for an additional 80 wk. No differences were seen between any of the treated groups and controls. No association was observed between treatment and incidence of any particular tumor with the exception of adrenal cortex tumors, which were seen at lower incidence in DAAB-treated males. Malignant lymphomas originated most frequently in the spleen, mesenteric lymph nodes, and Peyer's patches, and were seen more frequently in females but not in excess of control values. Liver cell tumors occurred with very low frequency. (15 Refs)

HETEROCYCLIC AMINES

16. EFFECT OF METHYL SUBSTITUTION ON MUTAGENICITY OF 2-AMINO-3-METHYLIMIDAZO[4,5-F]QUINOLINE, ISOLATED FROM BROILED SARDINE.

Nagao M, Wakabayashi K, Kasai H, Nishimura S, Sugimura T
Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan
Carcinogenesis; 2(11):1147-1149 1981

The compound 2-Amino-3-methylimidazo[4,5-f]quinoline [I] is a potent mutagen isolated from broiled sun-dried sardine. [I] and its seven derivatives. (2 isomers, 1 demethylated derivative and 4 methyl-substituted derivatives), were tested for mutagenicity on Salmonella typhimurium TA98 and TA100 in the presence of S9 mix. 2-Amino-1,4-dimethylimidazo[4,5-f]quinoline was the strongest mutagen of these 8 compounds on TA98, giving 159,000 revertants/nmol (750,000 revertants/ug). The demethylated derivative, 2-aminoimidazo[4,5-f]-quinoline, had very weak mutagenicity, inducing only 55 revertants/nmol (200 revertants/ug). Compounds having a methyl group at position N-1 or N-3 of 2-aminoimidazo[4,5-f]quinoline were strong mutagens. The 1,5-dimethyl-derivative was more mutagenic than the 3,5-dimethyl-derivative. Introduction of a methyl group at position 4 and position 5 enhanced and reduced the mutagenicity, respectively. All the compounds tested were more mutagenic to TA98 than to TA100, but their relative orders of mutagenicity with TA98 and TA100 were the same. (Author abstract) (22 Refs)

REVIEWS AND OTHER RELATED STUDIES

17. COMPARATIVE NEOPLASTIC TRANSFORMATION RESPONSES OF BALB/3T3 CELLS, SYRIAN HAMSTER EMBRYO CELLS, AND RAUSCHER MURINE LEUKEMIA VIRUS-INFECTED FISCHER 344 RAT EMBRYO CELLS TO CHEMICAL CARCINOGENS.

Dunkel VC, Pienta RJ, Sivak A, Traul KA
Bureau Foods, Food and Drug Admin., Public Health Service, 200 C St., S.W., Washington, DC, 20204
JNCI; 67(6):1303-1315 1981

This study provides a preliminary comparative evaluation of the responses to a series of 49 chemicals, in in vitro transformation assays, of Balb/3T3 cells, Syrian hamster embryo cells, and Fischer 344 rat embryo cells infected with Rauscher murine leukemia virus. The chemicals assayed included aromatic amines; polycyclic aromatic hydrocarbons; alkylating agents; nitrosamines, hydrazines, and related compounds; heterocyclic compounds; amides, ureas, and acylating agents; inorganic compounds; and hormones. In all three assays 37 of the chemicals were tested. The most uniform test responses were obtained with the polycyclic aromatic hydrocarbons and inorganic compounds. With the other groups of chemicals, more variation in response was observed. This study expands the base of information on the potential of these in vitro transformation systems, and the lack of responses with some of the chemicals underscores the need for incorporation of exogenous metabolic activating systems into these assay systems. (Author abstract) (20 Refs)

18. A MICROSUSPENSION ADAPTATION OF THE BACILLUS SUBTILIS 'REC' ASSAY.

McCarroll NE, Keech BH, Piper CE
Dept. Toxicology, Hazleton Lab. America, Inc., 9200 Leesburg Turnpike, Vienna, VA, 22180
Environ Mutagen; 3(6):607-616 1981

Sixty-six high mw or poorly soluble compounds were tested for mutagenicity in the Bacillus subtilis 'rec' assay. Six of 13 mutagenic aromatic amines were detected as preferential inhibitors of B subtilis M45. Nine polycyclic aromatic hydrocarbons, including benzo(a)pyrene, 3-aminopyrene, 7,12-dimethylbenz(a)anthracene, and 3-methylcholanthrene, which do not elicit a genotoxic effect in Escherichia coli, were found to have preferential inhibitory activity towards M45. Anthracene, phenanthrene, and pyrene were inert. Dimethylnitrosamine and diethylnitrosamine both diminished growth of M45, as did a variety of other nitrosamines and hydrazines. The noncarcinogenic antimetabolite 5-fluoro-2'-deoxyuridine was genotoxic to M45. Acetamide, ethyl carbamate, methyl carbamate, and thiourea were inactive against M45, confirming results obtained using E Coli MSA and other microbial systems. All mutagenic alkylating agents except Captan were genotoxic in M45. In contrast to results obtained in E coli, 4-nitrobiphenyl was active in the M45 system. The lack of response in E coli may result from cell wall impenetrability of the compound. The contribution of solvents to toxicity in the B subtilis and E coli MSA systems is discussed. (13 Refs)

19. IDENTIFYING HUMAN CELLS CAPABLE OF METABOLIZING VARIOUS CLASSES OF CARCINOGENS.

Aust AE, Antczak MR, Maher VM, McCormick JJ
Dept. Microbiology, Michigan State Univ., East Lansing, MI, 48824
J Supramol Struct; 16(3):269-279 1981

Metabolism of tritiated benzo(a)pyrene (BP) to aqueous-acetone soluble forms and inhibition of cellular DNA synthesis were used to identify human cells capable of metabolizing various classes of carcinogens. Hydrocarbon-metabolizing activity assay (HMAA) and DNA synthesis inhibition assa y were optimized and the results on 15 human epithelial cell lines were compared. Four classes of carcinogens were examined: polycyclic hydrocarbons (PH), aromatic amines (AA), heterocyclic hydrocarbons, and nitrosamines. Each of the classes was activated by one or more cell lines. Cells with very low metabolizing activity, such as NF, showed little or no cytotoxic response when exposed to BP at concentrations up to 30 uM for 48 hr. Biological results (cytotoxicity, mutagenicity, and DNA binding) suggest that the HMAA is a useful prescreen for identifying human cells that metabolize BP to biologically active forms. Cells that appeared capable of metabolizing PH or AA according to the methods were found to produce metabolites which were cytotoxic to cocultivated human xeroderma pigmentosum fibroblasts after 48 hr exposure to the carcinogen. (28 Refs)

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ANILINES AND EXTENDED ANILINES

1. URINARY METABOLITES OF 3,3'-DICHLOROBENZIDINE AND THEIR MUTAGENICITY.

Tanaka KI
Toray Shiga Hosp., 7-35, Sonoyama 2-chome, Otsu 520, Japan
Sangyo Igaku; 23(4):426-427 1981

3,3'-dichlorobenzidine (DCBZ) was administered to rats, urinary metabolites of the DCBZ, 3,3'-dichloro-N-acetylbenzidine (N-AcDCBZ) and 3,3'-dichloro-N,N'-diacetylbenzidine (NN'-AcDCBZ), were observed in the urine of the rats, and mutagenicity of the DCBZ, N-AcDCBZ, and NN'-AcDCBZ was investigated using Salmonella typhimurium TA 98 and TA 100 and a revertant mutagenicity test. Spectrographic pure DCBZ was administered po (20 mg) to five rats (Group 1), per trachea (10 mg) to five (Group 2), and pc (200 mg) to five (Group 3); five rats were not administered the DCBZ. DCBZ, N-AcDCBZ, and NN '-AcDCBZ were detected with both gas chromatography and high pressure liquid chromatography in the urine of Group 1 and 2 rats. Only NN'-AcDNBZ was observed in the urine of Group 3 rats. With the aid of Ames test, mutagenic activity of 1 ml urine samples containing N-acetyl

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DCBZ metabolites was shown to increase with the concentration of the metabolites in the urine samples from the Group 1 and 2 rats, but no mutagenic activity was observed for the 1 ml samples from the Group 3 rats. The mutagenic activity of the NN'-AcDCBZ was much lower than that of the DCBZ or the N-AcDCBZ. These techniques were thought to be applicable for study of mechanisms of carcinogenicity of these metabolites as well as for biological monitoring of the substances. (7 Refs) (In JPN)

2. INDUCTION OF PROSTATE CANCER BY 3,2'-DIMETHYL-4-AMINOBIPHENYL (DMAB) IN RATS (MEETING ABSTRACT).

Katayama S, Fiala E, Reddy S, Rivenson A, Silverman J, Williams GM, Weisburger JH

Department of Pathology, Osaka University Medical School, Osaka, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Prostate cancer induced by sc injections of DMAB, either 20 mg per kg body wt, once a wk for 42 wk or 50 mg per kg body wt, once a wk for 20 wk, were studied in F344 rats of 5 different experiments. Overall incidence of prostate cancer in 293 animals examined with DMAB was found in 95 (32%). Among them, 66 rats showed putative early lesions of cancer and 28 developed carcinoma in situ. Although the prostate with these lesions remained at microscopic level, there was one overt tumor, in which histologic examination revealed an invasive adenocarcinoma, but no metastases were recognized. None of the controls nor castrated animals developed prostate neoplasms. (no Refs)

FLUORENAMINES: IN VIVO

3. SEQUENTIAL CHANGES IN HISTOCHEMICAL LOCALIZATION OF EPOXIDE HYDROLASE AND GAMMA-GLUTAMYL TRANSPEPTIDASE DURING HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Noda K, Fukumoto Y, Oki K, Takemoto T

1st Department Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The subject of this study is the clarification of roles about microsomal epoxide hydrolase (EH) in promotion stage of chemical carcinogenesis. After diethylnitrosoamine (DEN) (200 mg/kg, ip), partial hepatectomy and 2-acetylaminofluorene (2-AAF) feeding (0.02%, 2 wk) were done. From 1 to 8 wk rats were sacrificed and liver tissues were fixed with ethanol. By means of peroxidase-antiperoxidase method, the changes of EH localization were studied, and also gamma glutamyl transferase (GGT) was examined by the consecutive liver tissue sections. From 2 wk the regression of EH was recognized in each focus. And in major parts of foci, GGT localized in those EH-negative areas as if in compensation. Furthermore, the change in a remodeling stage was studied with the intermittent 2-AAF feeding (0.05%) regimen. The different localization of the two kinds of marker enzymes is discussed. (no Refs)

4. EUCHROMATIN PROTEIN PHOSPHORYLATION AND NEOPLASTIC TRANSFORMATION (MEETING ABSTRACT).

DeLuca C, Smith GJ

Department of Pathology, University of New South Wales, New South Wales, Australia

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Non histone chromosomal proteins (NHCP) are thought to have a specific gene regulatory function. Indentification and characterization of phosphorylated NHCP may provide useful cellular markers for the early onset of neoplasia and may elucidate mechanisms of neoplasia. The experiment design involves an analysis of euchromatin protein alteration during the initial and promotional stages of chemical carcinogenesis as outlined in the Solt-Farber regime. Diethylnitrosamine (DEN) is used as the initiating agent and promoting is achieved through the dietary administration of 2-acetylaminofluorene accompanied by a non-specific growth stimulus-partial hepatectomy. The DNAse I prepared soluble transcriptionally active (euchromatin) fraction is extracted from purified nuclei, labelled with [32P] orthophosphate in primary cell suspension culture. The chromatin proteins are analyzed by two dimensional polyacrylamide gel electrophoresis and autoradiography. Preliminary observations indicate that following a single dose of DEN (200 mg/kg ip), there is acute histological damage to nuclei at one wk and complete recovery within three wk. Electron micrographs of purified nuclei confirmed these findings. Furthermore, electrophoretic analysis of control and DEN treated animals using Coomassie blue visualization of proteins, resulted in the detection of several proteins, not evident in the control animals. (no Refs)

5. EXPRESSION OF THE TUMOR ALDEHYDE DEHYDROGENASE PHENOTYPE DURING 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOCARCINOGENESIS.

Lindahl R, Evces S, Sheng WL
Biochemistry Program, Univ. Alabama, University, AL, 35486
Cancer Res; 42(2):577-582 1982

In aromatic amine-induced rat hepatomas, the aldehyde dehydrogenase (AlDH) phenotype is qualitatively and quantitatively different from that of normal liver. To identify the mechanism(s) underlying the expression of the tumor-specific AlDHs, we have followed the time course of appearance of the new phenotype during hepatoma formation in Sprague-Dawley rats following brief dietary exposures to 2-acetylaminofluorene (0.02%; 32 days). Tumor promotion by phenobarbital (0.05% in the diet) was also used to compare th e effects of a variety of tumor induction protocols on the AlDH phenotype. No change in the AlDH phenotype is detectable by total activity assay, gel electrophoresis, isoelectric focusing, or immunochemical methods during or following exposure to carcinogen cr promoter until tumors are grossly observed in liver. Concomitant with tumor appearance, the tumor-specific AlDH phenotype appears. The phenotypic change is limited to the tumor; morphologically and histologically normal liver directly adjacent to the tumor and normal lobes of a tumor-bearing liver do not possess the tumor AlDH phenotype. No correlation exists between tumor size and the degree of deviation of the AlDH phenotype from normal. Nor is there any correlation between the degree of AlDH phenotype deviation and the histology of the various tumors observed. We conclude that the tumor-specific AlDH phenotype is not associated with altered liver metabolism due directly to carcinogen or promoter exposure. Rather, the mechanism of this phenotypic change requires that transformation-associated, stable genetic changes occur in the cells affected by carcinogen that are later expressed as the altered AIDH phenotype. (Author abstract) (22 Refs)

6. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS; SUMMATION VERSUS PROMOTION EFFECTS (MEETING ABSTRACT).

Katayama S, Ohmori T, Williams GM
Department of Pathology, Osaka University Medical School, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The enhancement of the effects of a carcinogen by a subsequently administered chemical is routinely regarded as evidence of promotion. On the other hand, as an extension of summation of multiple irreversible alterations produced by the total dose of a carcinogen, Nakahara and others have shown that sequential administration of two different carcinogens will produce a summation effect. Thus, the operational definition of a promoter based solely upon its enhancing effect in a protocol of sequential administration becomes questionable. To examine this problem, we undertook a comparison of the effects of phenobarbital (PB) versus diethylnitrosoamine (DEN) when each was given after 2-acetylaminofluorene (AAF). The effects of PB and DEN were comparable, however DEN exerted a greater enhancing effect on the oncogenic outcome of AAF exposure than PB. (no Refs)

7. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYL-ACETAMIDE INDUCED RAT LIVER LESIONS (MEETING ABSTRACT).

Tanaka T, Mori H, Nishikawa A, Takahashi M
Department of Pathology, Medical Gifu University, Gifu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Comparison of enhancing effects of phenobarbital (PB) and barbital (B) in hepato tumorigenesis was examined by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats of 2 mo old were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. Remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% B diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin or iron stain specimen/cm2 of the liver space at 16 wk of Group I remarkably decreased compared to that at termination of FAA feeding. However, the number of Group II or III was similarly maintained at 8 and 16 wk and the number at 16 wk of both groups was significantly higher than that of Group I. These data show that B like PB could be an enhancer in hepatotumorigenesis. (no Refs)

8. INDUCTION, CHARACTERIZATION AND ISOLATION OF PRENEOPLASTIC HEPATOCYTES AFTER COMBINED TREATMENT WITH 2-ACETYLAMINOFLUORENE AND FERRIC NITRILOTRIACETATE.

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Boll Soc Ital Biol Sper; 57(16):1722-1726 1981

Male rats (Sprague-Dawley, 80-90 g) were administered for 8 wk ferric nitrilotriacetate (Fe-NTA; 0.5 ml/100 g/day ip) and 2-acetaminofluorene (2-AAF; 300 mg/kg standard diet without antioxidants). Control animals were administered the same dose of Fe-NTA. One wk after the end of treatment, liver was perfused in situ with Hanks soln without Ca. Two liver tissue specimens were removed for histological and histochemical testing. Liver perfusion was followed with collagenase, and at the end of perfusion, hepatocytes were removed by bland mechanical treatment. Part of the suspension was used to prepare smears and for biochemical testing, the rest was further purified. Partial separation of different cells was accomplished by isopycnic gradient separation. Combined administration of Fe-NTA and 2-AAF induced formation of small nodules or areas made of HC without iron that can be easily identified due to the absence of pigment. Gamma glutamyltranspeptidase activity was demonstrated in areas without iron, while glucose-6-phosphatase activity disappeared. (15 Refs) (In ITA)

9. HEPATOCARCINOGENICITY OF DIETHYLSTILBESTROL (DES) IN RATS (MEETING ABSTRACT).

Kamiya K, Seyama T, Kodama Y, Numoto M, Yokoro K
Department of Pathology, Hiroshima University, Hiroshima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Despite the demonstration of carcinogenicity of DES in estrogen-susceptible tissues of some animal species, little is known about its carcinogenic effect in the liver. Castrated W/Fu rats treated with DES alone developed tumors of the liver (HT) in 30% of animals. By a combined treatment of DES and N-nitrosobutylurea (NBU) which is not hepatocarcinogen itself, HT incidence is much increased in several rat strains. In this system, androgen had no promotive effect in HT induction and the incidence correlated well with the dosage of DES. While castration prevents N-2-fluorenylacetamide (2-FAA) induced hepatocarcinogenesis, a combined treatment of 2-FAA and DES in castrated rats remarkably increased the incidence and tumor size of HT and shortened the latent period, suggesting the promotive effect of DES on the growth of transformed cells initiated by 2-FAA. Those results indicate that DES is a complete carcinogen with activities stronger in promotion than in initiation. (no Refs)

10. RESISTANCE OF PRENEOPLASTIC LIVER CELLS OF RATS TO MEMBRANE-ACTIVE AGENTS (MEETING ABSTRACT).

Sawada N, Furukawa K, Tsukada H
Department of Pathology, Cancer Research Institute, Sapporo Medical College, Sapporo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Normal and 2-acetylaminofluorene (2-AAF) induced preneoplastic (PN) liver cells of rats were isolated by collagenase perfusion methods. The cell suspension was mixed with phalloidin and incubated for 20 min at 37C. Percentage of the cells forming cytoplasmic blebs (phalloidin-sensitive cells) was smaller for PN cells than for normal cells. After 3 hr culture, the cells were incubated with phalloidin for 20 min, then they were fixed and stained for gamma-glutamyl transpeptidase (GGT). Bleb-formation of GGT-positive PN cells was lower in incidence than that of GGT-negative PN cells. Ca-ionophore, A23187, was added to the 24 hr culture and incubated for 1 hr. There was no difference in the cell viability between PN and normal cells, when determined by trypan blue exclusion test. D-galactosamine was added at the beginning of the culture in the presence of 3.6 mM Ca++. Viability of the cells after 24 hr of the culture was higher for PN cells than for normal cells. It is suggested that resistance of PN cells to hepatotoxins includes alterations in the cell membranes. (no Refs)

11. IN VIVO SKIN PENETRATION STUDIES OF 2,4-TOLUENEDIAMINE, 2,4-DIAMINOANISOLE, 2-NITRO-P-PHENYLENEDIAMINE, P-DIOXANE AND N-NITROSODIETHANOLAMINE IN COSMETICS.

Marzulli FN, Anjo DM, Maibach HI
Natl. Acad. Sciences, Washington, DC
Food Cosmet Toxicol; 19(6):743-747 1981

In vivo skin-penetration capacities of five substances found in cosmetics were studied in humans, monkeys, and swine. Skin penetration of 2,4-toluenediamine was greatest and that of 2,4-diaminoanisole least. Rough estimates of absorbed amounts under normal cosmetic use are given. (21 Refs)

12. LAPAROSCOPIC CHANGES OF THE LIVER DURING HEPATOCARCINOGENESIS FED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE OR 2-FLUORENYLACETAMIDE (MEETING ABSTRACT).

Numa Y, Okita K, Ando K, Fukumoto Y, Kodama T, Takemoto T
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The hyperplastic liver nodule has been focused as the precancerous lesion in rats during hepatocarcinogenesis. However, there is not any direct evidence that hepatoma is exactly induced in this nodule. Therefore, we applied the laparoscopic method to observe the course during hepatocarcinogenesis. The small diameter fiberscope (diameter 4 mm) and rigid laparoscope were made by the courtesy of Machida Co (Tokyo). Moreover, a biopsy method under direct vision was devised for the consecutive histological study of the nodules. Tentatively, laparoscopy revealed 2 kinds of nodules showing red or gray with or without vessels on their surface. Moreover, the biopsied specimen was sufficient to analyze biochemical multiplicity of the nodules. (no Refs)

FLUORENAMINES: IN VITRO

13. STARVATION OF ARGININE AND GLUTAMINE SENSITIZES HUMAN DIPLOID CELLS TO THE TRANSFORMING EFFECTS OF N-ACETOXY-2-ACETYLAMINOFLUORENE.

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Carcinogenesis; 2(12):1303-1310 1981

We have examined the influence of the method of synchronization on the transformation of normal human diploid fibroblasts treated in mid-S phase with N-acetylaminofluorene (N-Ac-AAF), and on the subsequent kinetics of the removal of carcinogen damage. At early times posttreatment, the transformation frequency in cultures synchronized by a 24 hr starvation for arginine and glutamine was enhanced over that of cultures synchronized by release from confluence. In cells synchronized by either method, transformation was enhanced at all times when the cells were incubated after treatment in medium containing high concentrations of nonessential amino acids, vitamins and serum. Synchronized cells treated with 3 uM [3H]N-Ac-AAF in mid-S removed significantly less DNA damage than cultures treated and held under confluent, noncycling conditions. Cells synchronized by amino acid starvation removed less damage than cells synchronized by release from confluence. S-phase treatment of synchronized cells resulted in a dose-dependent delay of DNA replication. The early, rapid phase of repair was temporally correlated with the delay in S-phase progression. We conclude from these data that synchrony achieved by amino acid starvation renders human cells more sensitive to N-Ac-AAF-induced transformation in vitro than does that achieved by release from density-inhibition of growth. The S-phase treated, cycling cells lost only about 10% of their initial carcinogen damage before reinitiation of treatment-delayed bulk DNA synthesis. These results support the hypothesis that the persistence of carcinogen damage in replicating DNA may be an important factor in cell transformation. (Author abstract) (46 Refs)

14. METABOLISM AND BINDING OF BENZO(A)PYRENE AND 2-ACETYLAMINOFLUORENE BY SHORT-TERM ORGAN CULTURES OF HUMAN AND RAT BLADDER.

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Cancer Res; 42(2):642-648 1982

The ability of organ cultures of normal human and rat bladder to metabolize the polycyclic hydrocarbon, benzo(a)pyrene (BP), and the arylamine, 2-acetylaminofluorene, has been studied. Cultures were maintained for 0 to 6 days in a chemically defined medium before incubation with [3H]BP (0.3 to 0.5 uM) or 2-[14C]acetylaminofluorene (18 to 25 uM) for 24 hr. Ethyl acetate-soluble and water-soluble metabolites were produced from both compounds by both species. The ethyl acetate extracts from [3H]BP-treated human cultures contained 9,10-dihydro-9,10-dihydroxybenzo(a)pyrene, 7,8-dihydro-7,8-dihydroxybenzo(a)pyrene, and 3-hydroxybenzo(a)pyrene. Rat bladder cultures produced similar metabolites but in slightly different proportions. Ethyl acetate-soluble products of 2-[14C]acetylaminofluorene from human cultures contained 7-hydroxy-2-acetylaminofluorine, 9-hydroxy-2-acetylaminofluorene, 2-aminofluorene, and N-hydroxy-2-acetylaminofluorene. Rat bladder cultures produced similar metabolites, but 2-aminofluorene was found in relatively higher proportion. Hydrolysis by beta-glucuronidase of the water-soluble products produced from both carcinogens gave ethyl acetate-extractable derivatives. These hydrolyzable glucuronide conjugates were relatively more abundant following metabolism of the carcinogens by the rat than by the human cultures. Covalent binding to DNA occurred with [3H]BP in both human (19.7 +-13 pmol/mg DNA) and rat cultures (22.8 +-8.6 pmol/mg DNA). As with other human tissues, considerable variation (50-fold) was observed between individuals. The results demonstrate that both human and rat bladder epithelium can metabolize known potent carcinogens and, in the case of BP, can effect covalent binding between the products of metabolism and the urothelial cell DNA. In theory, carcinogenesis in the urinary bladder could thus be initiated by carcinogens produced or excreted in the urine without the necessity for their prior metabolism elsewhere in the body. (Author abstract) (66 Refs)

15. ISOLATION AND PARTIAL CHARACTERIZATION OF MUTAGEN-SENSITIVE AND DNA REPAIR MUTANTS OF CHINESE HAMSTER FIBROBLASTS.

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Environ Mutagen; 3(1):53-64 1981

Isolation and partial characterization of several mutants of Chinese hamster cells, which are affected in their ability to repair DNA damage or in their sensitivity to radiation or chemical mutations, are discussed. Cells of a subclone of the V79 aneuploid cell line were mutagenized by combined treatment with 5-bromodeoxyuridine and blacklight, followed by UV irradiation. 3H-thymidine was incorporated in repair-proficient cells at high temperature (38.5 C) following UV damage. Cells were held in the cold (4.0 C) to induce radioactive thymidine killing. Repair-deficient and UV-sensitive cells which had survived and formed colonies at low temperature (34.0 C) were tested for recovery. Seventy-two surviving colonies were isolated from 2 x 10(7) cells plated for selection. Four colonies were selected for extensive study. Colony UVs-7 was slightly more sensitive to UV, but not sensitive to x-rays or N-acetoxy-2-acetylaminofluorene (NAc-AAF); this mutant exhibited a highly reduced level of unscheduled DNA synthesis (UDS), as compare to the parental line. UVs-40 and UVs-44 line colonies were sensitive to UV, x-ray, N-methyl-N-nitro-N-nitrosoguanidine, and NAc-AAF, but exhibited normal UDS. Line UVr-23 had enhanced UDS, was resistant to UV, but exhibited no difference in sensitivity to x-ray or NAc-AAF. These four mutants are all stable, and may be useful for the study of mammalian DNA repair processes and mechanisms of mutagenesis. (38 Refs)

16. METABOLISM OF 2-ACETYLAMINOFLUORENE IN PRIMARY RAT HEPATOCYTE CULTURES.

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J Toxicol Environ Health; 7(1):93-106 1981

The kinetics of 2-acetylaminofluorene (AAF) metabolism are investigated at various doses and with varying cell culture conditions. Primary cultures of 2 x 10(6) Sprague-Dawley rat hepatocytes metabolized all of a dose of 137 ng of 13.7 ug AAF during 12-24 hr of incubation. At higher concentrations of AAF per 2 x 10(6) cells, the rate of metabolism diminished and water-soluble metabolites appeared at 70% the rate at lower doses. Presumptive covalently bound AAF residues reached a max of 5% of the adminstered 137 ng per 2 x 10(6) M cells. The rate of appearance of water-soluble AAF metabolites was stimulated by the addition of hormones to the culture medium, correlating with the enhanced cytochrome P-450 levels in hormone-treated cells. With 10(-4) M SKF 525A, the metabolism of AAF was diminished 50%; with 10(-3) M, it was eliminated. With 40 ug AAF per 2 x 10(6) cells, 31% of AAF was recovered as water-soluble products after 24 hr. The cells could then metabolize a subsequent 40-ug dose at an undiminished rate. Thus, primary rat hepatocyte cultures constitute an in vitro model for the quantitative study of the cellular disposition of a chemical carcinogen in its presumptive target cell. (43 Refs)

17. METABOLIC ACTIVATION OF CARCINOGENS IN THE SALMONELLA MUTAGENICITY ASSAY BY HAMSTER AND RAT LIVER S-9 PREPARATIONS.

Raineri R, Poiley JA, Plenta RJ, Andrews AW
Chemical Carcinogenesis Program, Fredrick Cancer Res. Center, Frederick, MD, 21701
Environ Mutagen; 3(1):71-84 1981

In the Salmonella mutagenicity assay, mutagenicity of the known carcinogens 2-acetylaminofluorene (AAF), 2-aminoanthracene (AA), 3-methylcholanthrene (MCA), benzo(a)pyrene (BP), and diethylnitrosamine (DEN) were directly compared using either uninduced or phenobarbital (PB)- or Aroclor (AC)-induced liver S-9 preparations from both male and female hamsters and rats. Effects of different concentrations of the S-9 protein were studied. Mutagenicity data were compared with the aryl hydrocarbon hydroxylase (AHH) and BP-4,5-epoxide hydrase (EH) activities of the liver S-9 preparations, and the levels of binding of BP metabolites to DNA were measured. The preparations from hamster liver were consistently more effective than those from rat liver for the activation of AAF, AA (except for AC-induced preparations), MCA, and DEN to their mutagenic forms. Induced preparations from rats were more active than those from hamsters when using BP. With the aromatic amines (AAF and AA), a partial inhibition of mutagenicity occurred at the highest protein concentrations tested. Inverse relationship was observed with BP between protein concentration and number of revertants occurring in the presence of the preparation from PB- and AC-induced male and female rats. Relative order of activities of AHH and EH in preparations was AC-induced greater than PB-induced greater than uninduced. An exception was the liver S-9 preparation from AC-induced female rats, which induced no EH activity. Levels of binding of the metabolites of tritiated BP to calf thymus DNA were correlated with AHH levels except in the case of the preparation from PB-induced female rats, in which no binding was detected. (31 Refs)

18. ACTIVATION OF BENZO(A)PYRENE AND 2-ACETAMIDOFLUORENE TO MUTAGENS BY MICROSOMAL PREPARATIONS FROM DIFFERENT ANIMAL SPECIES: ROLE OF CYTOCHROME P-450 AND P-448.

Ioannides C, Parkinson C, Parke DV
Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Xenobiotica; 11(10):701-708 1981

The metabolic activation of benzo(a)pyrene and 2-acetamidofluorene to mutagens was studied with liver microsomal preparations from rat, guinea-pig, hamster and mouse, untreated or pretreated with phenobarbitone or 3-methylcholanthrene.

Liver microsomal preparations from all animal species activated benzo(a)pyrene, that from mouse being the most efficient. Similarly, microsomal preparations from guinea-pig, hamster and mouse could activate 2-acetamidofluorene, but that from rat exhibited very weak activity. Activation of benzo(a)pyrene into mutagenic intermediates by liver microsomal preparations was increased for all animals except mouse by pretreatment with 3-methylcholanthrene. In contrast, pretreatment with phenobarbitone decreased the activation by microsomal preparations from all species. Activation of 2-acetamidofluorene by liver microsomal preparations from rat and guinea-pig, but not mouse and hamster, was increased by pretreatment of the animals with phenobarbitone. Pretreatment with 3-methylcholanthrene decreased the activation of this carcinogen by microsomal preparations from all species. The metabolic activation of benzo(a)pyrene is catalyzed by cytochrome P-448 but not cytochrome P-450. The activation of 2-acetamidofluorene to mutagens may involve, in addition to the mixed-function oxidases, other microsomal enzyme systems. (Author abstract) (29 Refs)

19. URINE-MEDIATED AMES TEST: INTERACTIONS.

Aeschbacher HU, Ruch E
Res. Dept., Nestle Products Technical Assistance Co. Ltd., CH-1350 Orbe, Switzerland
Mutat Res; 103(2):127-131 1982

The vol of urine extracted for use with the Ames test for mutagenicity has an important influence on the results. Urine collected from six human subjects (who neither smoked, nor consumed alcohol or stimulatory beverages, nor medicines) was combined; half of the pooled urine was subjected to beta-glucuronidase (BG) enhancement for 24 hr at 37 C, while the other half was stored at 4 C. Volumes of 0.5, 1.5, and 3.0 liters were passed through 14.5 x 3.5 cm plastic columns containing purified XAD-2 resin. Dimethyl sulfoxide-dissolved residues were added to plates of Salmonella T98 in amounts from 25-100 ul, and mutagenicity scored by number of revertants in two series: one with 2-acetylaminofluorene (2AF) and S9 activation and one with daunomycin (DM) but no S9. Mutagenicity was inhibited in a volume-dependent way in both series, and was more pronounced for the BG-treated urine. When urine extracts from urine without BG enhancement were plated with the mutagens (2AF and DM) the inhibitory effect occurred only with the extract from the highest vol of urine (3 liters). (8 Refs)

20. ALTERNATIVE CONFORMATIONS OF DNA MODIFIED BY N-2-ACETYLAMINOFLUORENE.

Grunberger D, Santella RM
Cancer Center/Inst. Cancer Res., Dept. Biochemistry, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(3):231-244 1981

In vitro studies are presented of three alternative conformations of DNA modified by carcinogens: conformation of N-acetylaminofluorene (AAF) DNA; conformation of N-(deoxyguanosin-8-yl)-1-aminofluorene; and conformation of AAF-modified poly(dG-dC):poly(dG-dC). (38 Refs)

OTHER FUSED RING AMINES

21. DDT ACCELERATION OF MAMMARY GLAND TUMORS INDUCED IN THE MALE SPRAGUE-DAWLEY RAT BY 2-ACETAMIDOPHENANTHRENE.

Scribner JD, Mottet NK
Pacific Northwest Res. Foundation, 1124 Columbia St., Seattle, WA, 98104
Carcinogenesis; 2(12):1235-1239 1981

The compound 2-Acetamidophenanthrene (AAP) yields adducts to rat liver DNA and RNA in amounts comparable to those found for the potent hepatocarcinogen 2-acetamidofluorene, but is not hepatocarcinogenic. This suggested that AAP might initiate liver tumors, but was incapable of causing their progression to a detectable state. To test this hypothesis, the protocol devised by Peraino was used, in which 21-day-old male Sprague-Dawley rats were fed 0.02% AAP in a grain diet for 3 wk. This was followed by long-term feeding of 0.05% 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT). The mean latent period of all tumors (primarily mammary tumors) was reduced about 6 mo by the DDT feeding. No tumors were found in rats treated with DDT only. Livers in all animals appeared normal at autopsy or on laparotomy, and showed barely detectable signs of toxicity upon histological examination. Thus, we have found that a once wide-spread environmental chemical acts as a tumor accelerator on a major target for human tumors. Because this finding is in the male rat, the significance of this result for breast cancer in women is uncertain. (Author abstract) (15 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

22. UNSCHEDULED DNA SYNTHESIS INDUCED BY 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, AND THEIR DERIVATIVES IN PRIMARY CULTURES OF RAT AND MOUSE HEPATOCYTES.

Watanabe HK, Hashimoto Y
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):930-936 1981

The ability of carcinogenic and non-carcinogenic aminoazo dyes to induce unscheduled DNA synthesis (UDS) in primary cultures of hepatocytes of three strains of rats and two strains of mice was examined by means of microautoradiography. Azo dyes tested were 4-aminoazobenzene (AAB) and four of its ring methoxyl (MeO) derivatives, their N-hydroxy (N-OH) derivatives, N-methyl-4-aminoazobenzene (MAB) and its N-benzoyloxy derivative, and N,N-dimethyl-4-aminoazobenzene (DAB). All carcinogenic aminoazo dyes (AAB, 3-MeO-AAB, 4'-MeO-AAB, MAB and DAB), but not the non-carcinogenic dyes (2-MeO-AAB and 2,5-diMeO-AAB), induced UDS in rat hepatocytes as well as mouse hepatocytes. N-Hydroxy derivatives of AAB and its 3-and 4'-MeO derivatives elicited higher levels of UDS than did the corresponding mother aminoazo dyes. N-OH-2,5-MeO-AAB was as inactive with rat hepatocytes as the mother dye. N-OH-2,5-diMeO-AAB, however, elicited a definite level of UDS, in contrast to the mother 2,5-diMeO-AAB. N-Benzoyloxy-MAB, a prototype compound of the ultimate carcinogenic metabolite of MAB, was as active as the mother MAB. N-OH-3-MeO-AAB induced UDS more rapidly than did 3-MeO-AAB. The UDS elicited by 3-MeO-AAB was found to end within a few hours after releasing the hepatocytes from the azo dye. (Author abstract) (33 Refs)

23. A COMPARISON OF THE CARCINOGEN-DNA ADDUCTS FORMED IN RAT LIVER IN VIVO AFTER ADMINISTRATION OF SINGLE OR MULTIPLE DOSES OF N-METHYL-4-AMINOAZOBENZENE.

Tillis DL, Straub KM, Kadlubar FF
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Chem Biol Interact; 38(1):15-27 1981

The compound N-methyl-4-aminoazobenzene (MAB) is believed to be metabolized in the liver to an electrophilic N-sulfonyloxy ester which binds covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. A single dose of MAB is not sufficient for complete carcinogenic activity, so we sought to identify the MAB-DNA adducts present in rat liver after multiple oral doses of [3H]MAB. The MAB was administered by intubation at a level of 0.2 mmol/kg for 1, 3 or 4 doses and animals were sacrificed at 8 hr after the last dose. Hepatic DNA was isolated by extraction and hydroxylapatite chromatography and was enzymatically hydrolyzed to MAB-mononucleoside adducts, which were quantitated by high pressure liquid chromatography (HPLC). After three doses, N2-dG, C8-dG, and an unknown adduct were detected. By four doses, these accounted for 51%, 25% and 23% of the total adducts. This data is consistent with rapid removal of the C8-dG derivative and the relative persistence of the N2-dG and the unknown adduct. The latter was shown to exhibit chromatographic and pH-dependent solvent partitioning properties that were identical to a product also present in DNA treated with the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene. Analysis of this adduct by field desorption mass spectrometry and, after perdeuteromethylation, by electron mass spectrometry, indicated the structure to be a deoxyadenosin-N6-yl derivative substituted through an aromatic ring of MAB. Further analysis of 270 MHz 1H-NMR spectroscopy allowed complete assignment of the MAB and adenyl resonances and was uniquely consistent with a 3-(deoxyadenosin-N6-yl)-MAB structure. Since this persistent adduct is potentially mutagenic due to possible tautomeric equilibria between the N6-amino and N6-imino structures, it may represent an initiating lesion in MAB hepatocarcinogenesis. (26 Refs)

24. A STUDY ON THE LOST NUCLEAR RNA IN AZODYE-INDUCED HEPATOMA (MEETING ABSTRACT).

Akao M, Kuroda K
Department of Toxicology and Experimental Pathology, Research Institute Chemobiodynamics, Chiba University, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 198 1, Sapporo, Japan. The Association 415 pp., 1981.

DNA-RNA competitive hybridization study with the use of terminally 32P-labeled nuclear RNA (nRNA) indicated definitely the loss of some nRNA species in 3'-Me-dimethylaminoazobenzene (DAB) induced hepatoma. No such deletion was found in the livers of rats fed 3'-Me-DAB, alone or in combination with phenobarbital. The nRNA species that were present in liver and lost in hepatoma were then fractionated. The pertinent RNAs were found to exist among those whose sedimentation coefficients were less than 14S under sucrose density gradient centrifugation, and polyacrylamide gel electrophoresis indicated that these RNAs were fast-moving low mol wt ones. (no Refs)

25. AMINO ACID CONJUGATION OF N-HYDROXY-4-AMINOAZOBENZENE DYES: A POSSIBLE ACTIVATION PROCESS OF CARCINOGENIC 4-AMINOAZOBENZENE DYES TO THE ULTIMATE MUTAGENIC OR CARCINOGENIC METABOLITES.

Hashimoto Y, Degawa M, Watanabe HK, Takada M
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama Sendai 980, Japan
Gan; 72(6):937-943 1981

The activation process of N-hydroxy-4-aminoazobenzene (N-HO-AAB) dyes, proximate mutagenic or carcinogenic metabolites of AAB dyes, to the ultimate mutagenic or carcinogenic metabolites was studied by the use of an amino acid conjugation (aminoacylation) system catalyzed by yeast seryl-tRNA synthetase and [3H]ATP. A potent mutagen, N-hydroxy-3-methoxy-AAB (N-OH-3-MeO-AAB), as well as a non-mutagen, N-OH-2-MeO-AAB, were equally susceptible to N-O-serine conjugation. A weak mutagen, N-OH-AAB, and a moderate mutagen, N-OH-2,5-diMeO-AAB, were also susceptible to the aminoacylation, but to a lesser extent than the 2-or 3-methoxyl homologs. In contrast, N-hydroxy-N-methyl-4-aminoazobenzene and a moderate mutagen, N-OH-4'-MeO-AAB, were not susceptible to the aminoacylation. The ability of these N-OH-AAB dyes to bind with nucleic acid after serine conjugation was proportional to the susceptibility of the dyes to serine conjugation. Serine conjugates of N-OH-AAB dyes reacted with poly G, but not with poly A, poly C, or poly U, suggesting that the azo dyes selectively bind with guanine base of nucleic acids. The susceptibility of N-OH-AAB dyes to aminoacylation was compared with the carcinogenic, mutagenic and unscheduled DNA synthesis-inducing activities of these and the mother AAB dyes. (Author abstract) (29 Refs)

26. IN VITRO MUTAGENIC ACTIVATION OF 3'-HYDROXY-METHYL-N,N-DIMETHYL-4-AMINOAZOBENZENE (3'-CH2OH-DAB) (MEETING ABSTRACT).

Mori Y, Niwa T, Toyoshi K
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Our earlier experiment indicates that 3'-CH2OH-DAB, a new potent hepatocarcinogen, showed mutagenic activity towards Salmonella typhimurium TA-98 and 100 when tested with S-9. In order to clarify the mechanism of metabolic activation by S-9, effects of various factors known to influence xenobiotics metabolism on the mutagenic activities of 3'-CH(2)0H-DAB and 3'-Me-DAB were studied. The pretreatment of rats with polychlorinated biphenyl (PCB) and 3-methylcholanthrene (3-MC) and sodium phenobarbital (PB) showed that the ability of S-9 to activate these compounds was induced to the highest extent by PCB followed by 3-MC and PB, and the activation reaction required NADPH as a cofactor. On the other hand, these compounds showed less or no mutagenic activity in the presence of the S-105 fraction or S-9 from the livers of non-treated rats, those of mice and hamsters, and other organs of rats. These results indicate that microsomal enzymes in the S-9 fraction of rat liver is responsible for the metabolic activation of 3'-CH(2)0H-DAB and 3'-Me-DAB and that the carcinogenic specificity in regard to organs and species is similarly observed in their mutagenic effects with S-9. (no Refs)

27. DNA-DAMAGING ACTIVITY IN VIVO AND BACTERIAL MUTAGENICITY OF SIXTEEN AROMATIC AMINES AND AZO-DERIVATIVES, AS RELATED QUANTITATIVELY TO THEIR CARCINOGENICITY.

Parodi S, Taningher M, Russo P, Pala M, Tamaro M, Monti-Bragadin C
Dept. Oncology, Genoa Univ., Genoa, Italy
Carcinogenesis; 2(12):1317-1326 1981

Sixteen aromatic amines and azo-derivatives were studied. They were: benzidine; 2-acetylaminofluorene; 3'-methyl-p-dimethylaminobenzene; o-aminoazo-toluene; p-dimethylaminoazobenzene; 2,4-diaminotoluene; 4,4'-oxydianiline; 2,4-diaminoanisole; 4,4'-methylenedianiline; 2-naphthylamine; Auramine O; Rhodamine B; Ponceau MX; 1-naphthylamine; p-aminoazobenzene and aniline. The compounds were examined for their capability to induce alkaline DNA fragmentation in rat liver after treatment in vivo, for their mutagenicity in the Salmonella strains TA 98 and TA 100, for their acute toxicity and for their carcinogenicity in mice and rats. For each parameter a quantitative potency index was established, and the correlation existing amongst the different parameters investigated. Only mutagenicity in the strain TA 98 was slightly correlated with carcinogenic potency (r = 0.408). DNA fragmentation and toxicity were not correlated with carcinogenicity. A significant correlation was found between DNA fragmentation and toxicity (r = 0.539). No correlation was found between DNA fragmentation and mutagenicity. The lack of correlation between DNA fragmentation and carcinogenicity is in contrast with previous results obtained with a family of hydrazine derivatives and a group of nitroso compounds. For these two groups of chemicals correlation between DNA fragmentation and carcinogenicity existed, but not between carcinogenicity and mutagenicity in the Ames' test. It is suggested that short term tests can perform very differently for different classes of chemicals. (Author abstract) ,22 Refs)

28. MUTAGENICITY OF 4-AMINOAZOBENZENE, N-HYDROXY-4-AMINOAZOBENZENE, 4-NITROSOAZOBENZENE, 4-NITROAZOBENZENE, AND THEIR RING METHOXYLATED DERIVATIVES ON SALMONELLA.

Hashimoto Y, Watanabe HK, Degawa M
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(6):921-929 1981

The mutagenicity of 4-aminoazobenzene (AAB), N-hydroxy-4-aminoazobenzene, 4-nitroazobenzene, and their 2-, 3-, 4'-methoxyl and 2,5-dimethoxyl derivatives, and 2-methoxy-4-nitrosoazobenzene and 3-methoxy-4-nitrosoazobenzene were examined on Salmonella typhimurium TA98 and TA100. The activities of AAB dyes upon S-9 metabolic activation were related to their carcinogenic activities in the rat. The potent carcinogen 3-methoxy-4-aminoazobenzene was a potent mutagen for both tester strains. The moderate or weak carcinogens 4'-methoxy-4-aminoazobenzene and AAB were moderate or weak mutagens for one or both of the tester strains. The noncarcinogens 2-methoxy-4-aminoazobenzene and 2,5-dimethoxy-4-aminoazobenzene were non-mutagenic. In contrast to AAB dyes, N-hydroxy-4-aminoazobenzene dyes showed greater mutagenicity than the mother AAB dyes, without S-9 treatment. 4-Nitroazobenzene dyes and 4-nitrosoazobenzene dyes showed mutagenicity without S-9 treatment, and the activities were related to those of the corresponding N-hydroxy-AAB dyes. All 4-nitroazobenzene dyes were mutagenic in the presence of S-9, suggesting the production of mutagens other than N-hydroxy-AAB dyes by the S-9 treatment. The cytotoxicity of azo dyes to bacteria had no apparent relation to the mutagenic activity of the azo dyes. Incubation of 4-nitroazobenzene dyes with TA100 bacteria yielded N-hydroxy-AAB dyes. The synthesis and properties of new N-hydroxy-AAB dyes, 4-nitroazobenzene dyes and 4-nitrosoazobenzene dyes are described. (Author abstract) (27 Refs)

HETEROCYCLIC AMINES

29. EFFECT OF PHENOBARBITAL ON CHEMICALLY-INDUCED NEOPLASMS, MALFORMATIONS AND DOMINANT LETHALS IN MICE (MEETING ABSTRACT).

Gotoh H, Nomura T, Shibata K, Hata S, Enomoto T, Kusafuka T, Miyamoto S, Sakamoto Y
Department of Fundamental Radiology, Osaka University School of Medicine, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Phenobarbital (40-80 ug/g, sc) pretreatment of young adult and adult ICR/Jcl mice greatly diminished lung tumorigenesis initiated by urethane, furylfuramide (AF-2), and 7,12-dimethylbenz(a)anthracene (DMBA), while phenobarbital pretreatment enhanced embryo toxicities initiated by urethane, dimethyl-nitrosamine, 4-nitroquinoline-1-oxide, AF-2, and aminopyrine, but did not affect x-ray-induce d ones. DMBA-induced dominant lethals were also enhanced by phenobarbital pretreatment. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

30. CHRONIC HAZARDS ASSOCIATED WITH BENZIDINE CONGENER DYES IN CONSUMER DYE PRODUCTS.

Consumer Product Safety Commission
(c/o R. Fausett) Health Sciences, U.S. Consumer Product Safety Commission, Washington, DC, 20207
Fed Regist; 47(8,Book2):1843-1844 1982

The possibility of adverse health effects from consumer exposure to benzidine dyes, o-tolidine dyes, and o-dianisidine dyes (collectively termed 'benzidine congener dyes'), and the significant number of consumers that may be exposed to them, has prompted a proposal to regulate the use of such dyes. Alternatives to a petition to ban the dyes from consumer dye products include granting the petition, banning the use of benzidine dyes but not taking immediate action on o-tolidine dyes and o-dianisidine dyes, and denying the petition. (no Refs)

31. AN EPIDEMIOLOGICAL BASIS FOR CANCER CONTROL.

Armstrong B
NH and MRC Res. Unit in Epidemiology and Preventive Medicine, Univ. Western Australia, Dept. Medicine, Nedlands, Australia
Cancer Forum; 5(3):136-143 1981

Primary and secondary prevention of cancer, particularly cancer of the lung, breast, and colon and melanoma, which together account for greater than 40% of new cancer cases and premature mortality is discussed. Primary prevention aims at preventing cancer from occuring by ending exposure to the causal agent either by environmental or life type control. Lung cancer is attributable mainly to cigarette smoking; some cases result from occupational exposure. Breast cancer is associated with nulliparity, first full-term pregnancy at a comparatively late age, low parity, diet, radiation, post-menopausal estrogens, and oral contraceptives. Colon and rectal cancer are mainly related to dietary fiber deficiency and excess fat and meat consumption. Melanoma of the skin is due to exposure to UV radiation. Etiologies of other neoplasms are discussed: brain neoplasms (phenobarbitone use), prostate cancer (diet, cadmium exposure), stomach cancer (diet), leukemia (x-rays, benzene exposure, antineoplastic agent use), pancreatic cancer (diet, cigarette smoking), bladder cancer (occupational exposure to aromatic amines, cigarette smoking), and cervix cancer (sexual promiscuity). Dietary modification, cessation of smoking, and avoidance of excessive exposure to UV light was recommended. Screening methods involved in the secondary prevention of cancer include cervical cytology, proctosigmoidoscopy, and mammography at regular intervals for certain segments of the population. The choice between primary and secondary prevention of cancer is discussed. (20 Refs)

32. CHEMICALLY-INDUCED UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES: A COMPARISON WITH BACTERIAL MUTAGENICITY USING 218 COMPOUNDS.

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB
Div. Toxicology, Lilly Res. Laboratories, Greenfield, IN, 46140
Environ Mutagen; 3(1):11-32 1981

Hepatocyte primary culture (HPC)-DNA repair test using a relatively large number of compounds representing a wide variety of chemical classes is discussed. Over 200 compounds were tested for induction of unscheduled DNA synthesis (UDS) and the results were correlated with bacterial mutagenicity using a modified Ames test. A positive response was seen in both systems with many procarcinogens and ultimate carcinogens while compounds believed to be noncarcinogens were inactive. Recognized carcinogens/mutagens were readily detected by the two systems. Structurally realted noncarcinogens produced negative results in both systems. The modified Ames test and the HPC-UDS repair test were sensitive to compounds capable of interacting with DNA, and represent acceptable tests for genotoxic substances. The induction of UDS in hepatocytes showed good correlation with bacterial mutagenesis in response to polycyclic aromatic hydrocarbons, aromatic amines, biphenyls, nitrosamines, carbamates, azo-compounds, acridines, halogenated compounds, nitrosoureas, quinolines, pyridines, purines, pyrimidines, esters, and carbamates. Nitrocompounds although active in bacteria, were poor inducers of UDS. Results support the complementary and confirmatory nature of the tests for genotoxic chemicals and indicate the usefulness of the hepatocyte UDS system as a component in a battery of short-term predictive tests for mutagens/carcinogens. (45 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
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8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

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Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/07

JULY, 1982

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ANILINES AND EXTENDED ANILINES

1. HEPATIC MICROSOMAL METABOLISM AND COVALENT BINDING OF 2,4-DINITROTOLUENE.

Decad GM, Graichen ME, Dent JG
(c/o Dent) Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709

Toxicol Appl Pharmacol; 62(2):325-334 1982

The role of hepatic drug-metabolizing enzymes in the activation and detoxification of 2,4-dinitrotoluene (DNT), the effect of DNT treatment in vivo on hepatic enzyme activities in vitro, and in vitro metabolism and covalent binding of DNT to liver subcellular fractions were investigated. Adult male Fischer-344 inbred albino rats, four animals at each dose level, were treated with 70, 35, and 14 m g DNT/kg body wt by gavage

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for 5 consecutive days. A significant decrease in microsomal anaerobic nitroreductase activity, and a dose-related increase in liver cytosolic aerobic azoreductase activity were observed at the two higher doses. Treatment with DNT did not appreciably alter the pattern of DNT metabolism in hepatic microsomes or cytosol but did cause a slight increase in the rate of reductive metabolism under anaerobic conditions. No detectable metabolism of DNT occurred in liver microsomes from phenobarbital or Aroclor 1254-treated rats in the absence of NADPH and a regenerating system or with boiled microsomes. Very little covalent binding was detected in microsomes prepared from control or DNT-treated animals. Phenobarbital or Aroclor also markedly increased covalent binding. In microsomes from control and DNT-treated rats, the amount of covalent binding increased 5 to 10-fold as the oxygen concentration of the incubation decreased from 21 to 0%. In incubations performed for 30 min in nitrogen followed by 30 min in oxygen, less binding occurred than in either aerobic or anaerobic conditions alone. The low capacity of liver microsomes to reductively metabolize DNT under aerobic conditions suggested that gut flora are the primary site of reductive metabolism; an interaction between metabolism of DNT in gut flora and in the liver is apparently involved in toxicity. (29 Refs)

2. EFFECTS OF ORTHO-METHYL SUBSTITUENTS ON THE MUTAGENICITY OF AMINOBIPHENYLS AND AMINONAPTHALENES.

El-Bayoumy K, LaVoie EJ, Tulley-Freiler L, Hecht SS
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 90(4):345-354 1981

Mutagenic activity (MA) of five aminobiphenyls and five aminonaphthalenes was studied in Salmonella typhimurium strains TA100, TA1535, and TA1538 using the Ames assay. Metabolic activation was provided by S9 mix prepared from the livers of male Fischer-344 rats treated with Aroclor. MA was observed only in the presence of S9. Of the aminobiphenyls only 4-aminobiphenyl (4ABP) showed MA; 4ABP was active against TA1538 and TA100 but not against TA1535. 4-amino-3-methylbiphenyl (4A3M) showed greater MA than 4ABP against TA1538; 3-amino-4-methylbiphenyl (3A4M) and 3-aminobiphenyl (3ABP) showed no MA against TA 1538. 3A4M showed MA against TA100, while 3ABP did not. Results indicate that the presence of an ortho-methyl group enhances the MA of aminobiphenyls. Among the 2-aminonaphthalenes 2-amino-3-methylnaphthalene (2A3M) had the greatest MA against TA1538, followed by 2-amino-1-methylnaphthalene (2A1M) and 2-aminonaphthalene (2AN). 2AN had the greatest MA against TA1535. Neither 1-aminonaphthalene (1AN) nor 1-amino-2-methylnaphthalene had any MA against TA1538 or TA1535. 1AN showed weak MA against TA100. Results indicate that the presence of an ortho-methyl group inhibits base-pair MA and enhances frame-shift MA in aminonaphthalenes. (22 Refs)

3. PHENYLENEDIAMINES; RESPONSE TO INTERAGENCY TESTING COMMITTEE.

Hernandez JW
(c/o Douglas Bannerman) Industry Assistance Office (TS-799), Environmental Protection Agency, 401 M St., S.W., Washington, DC, 20460
Fed Regist; 47(5):973-983 1982

Section 4(e) of the Toxic Substances Control Act (TSCA) established an Interagency Testing Committee to recommend to the Administrator of the EPA a list of chemical substances and mixtures to be considered for the development of test rules under TSCA section 4(a). On May 28, 1980, the ITC recommended that the class phenylenediamines be considered for testing for their toxic effects on human health and the environment. EPA currently feels that toxicological data for the phenylenediamines and the exposure potential of 13 PDAs are sufficient to warrant proposing those 13 of the 47 chemicals recommended by the ITC for testing under section 4(a)(1)(A). EPA is considering the desirability of placing 34 additional phenylenediamines whose production is low or unknown or that are not currently in production, under other regulatory authority such as section 5(a) significant new use rule or a section 8(a) reporting rule. (Author abstract) (32 Refs)

4. MUTAGENIC EVALUATION OF CARCINOGENS AND NON-CARCINOGENS IN THE L5178Y/TK ASSAY UTILIZING POSTMITOCHONDRIAL FRACTIONS (S9) FROM NORMAL RAT LIVER.

Amacher DE, Turner GN
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CN, 06340
Mutat Res; 97(1):49-65 1982

The detection capabilities of the modified mouse lymphoma L5178Y TK+/- to TK-/- mutation assay were tested using 5% (vol/vol) S9 from rodents (usually Sprague-Dawley rat) which had not been treated with enzyme inducers. Most suspected carcinogens (7/10) caused a doubling of mutant frequency compared to solvent controls in a minimum of one experiment, at treatment levels permitting at least 61% cell survival; the exception was 4-nitrobiphenyl, which was considered mutagenic when two-sample loge t-test was done. Thioacetamide, a carcinogen, was negative for both the 5% noninduced S9 and the 10% Aroclor 1254-induced S9 tests. Dimethylcarbamyl chloride and glycidaldehyde were mutagenic in the absence of S9 but showed diminished activity in the presence of 10% S9. Styrene oxide was also mutagenic without S9. Noncarcinogens (6/8) were negative for mutagenicity in the present test; exceptions were chloracetic acid and p-aminophenol. (18 Refs)

5. MULTIPLE DRUG METABOLISM: P-NITROANISOLE REVERSAL OF ACETONE ENHANCED ANILINE HYDROXYLATION.

Bidlack WR, Lowery GL
Dept. Pharmacology and Nutrition, Univ. Southern California, Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033
Biochem Pharmacol; 31(3):311-317 1982

The unique effect of acetone on the p-hydroxylation of aniline was evaluated in microsomes prepared from control, phenobarbital- and 3-methylcholanthrene-pretreated animals. The existence of multiple forms of the hydroxylase was evaluated as an explanation of the acetone enhancement. Simultaneous metabolism of aniline in the presence of either p-nitroanisole (pNA) or ethylmorphine (EM) was evaluated to probe the participation of different mixed function oxidase systems. Aniline inhibited both N- and O-demethylation, while pNA and EM both inhibited p-hydroxylation of aniline. Acetone decreased the individual demethylation reactions, but enhanced aniline hydroxylation. In multiple drug reactions, acetone decreased N-demethylation and proportionately increased aniline p-hydroxylation. On the other hand, p-nitroanisole blocked the acetone enhancement of aniline metabolism. Kinetic evaluation of the acetone and p-nitroanisole effects on aniline metabolism indicated that each agent increased the apparent Km' by four- to five-fold for aniline in the hydroxylation reaction, but only acetone increased the Vmax'. From the Eadie-Scatchard analysis of the rates of aniline hydroxylation, acetone appeared to produce a biphasic increase in the hydroxylation above 0.75 mM aniline, even in the presence of pNA. Thus, multiple forms of the aniline p-hydroxylase are indicated by their altered activities in the presence of other drugs, and acetone seemed to specifically alter a species having a higher Km' for aniline. (Author abstract) (35 Refs)

6. POLYMERS OF DIPHENYLMETHANE DIISOCYANATE AND HYDROXY ALKYL ETHERS; APPROVAL OF TEST MARKETING EXEMPTIONS.

Gorsuch AM
(c/o R. Allison) Chemical Control Div., Office Toxic Substances, Environmental Protection Agency, Room E-206, 401 M St., SW., Washington, DC, 20460
Fed Regist; 47(31):6707-6708 1982

Approval of test marketing exemptions for polymers of diphenylmethane diisocyanate and hydroxy alkyl ethers to be used as a component and a coating of a synthetic running surface is reported. No health concerns exist for the test substances per se because of their high mol wt, but methylene dianiline may be formed if the diisocyanate is degraded in water. The exemption is subject to all conditions set out in the report.

7. NATIONAL STEWARDSHIP. PROTECTION OF WORKERS' HEALTH.

Chiriboga J
Dept. Health, San Juan, PR
Am J Ind Med; 2(1):1-2 1981

The concept of 'National Stewardship' for the protection of workers' health is discussed. Morally, scientists are held responsible for illness and/or deaths caused by actions they perform, even when these actions are not directly related to the final effect. While the manufacture of the carcinogen benzidine has been sharply curtailed in the United States, manufacture has increased in a directly opposite ratio in developing countries. Technology is exported, but the way to protect workers' health is not exported. (no Refs)

FLUORENAMINES: IN VIVO

8. ACUTE EFFECTS OF SELECTED HEPATOTOXIC AGENTS ON POLYRIBOSOMES AND PROTEIN SYNTHESIS IN THE LIVERS OF RATS FED PURIFIED DIETS CONTAINING HEPATOCARCINOGENS.

Sidransky H, Verney E
Dept. Pathology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Mol Pathol; 36(1):72-85 1982

This investigation was concerned with the effects of certain hepatocarcinogens ingested for long- or short-term intervals upon selected responses of rat liver to specific hepatotoxic stimuli. Rats fed ad libitum for long (3 to 45 wk) periods or force-fed for short (3 days) periods purified diets containing a single hepatocarcinogen, ethionine, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, or thioacetamide, were subjected to the acute administration of a single hepatotoxic agent, such as puromycin, actinomycin D, sparsomycin, hypertonic NaCl or CCl4, and hepatic protein synthesis (in vitro) and polyribosomal aggregation were evaluated. Relating to in vitro protein synthesis, in long-term experiments, puromycin induced less inhibition in the experimental groups than in the control (basal diet) group; and actinomycin D inhibited all groups similarly; while in the short-term experiments, puromycin induced less inhibition in the experimental groups than in the control group; actinomycin D inhibited the basal and ethionine groups more than the other groups; sparsomycin induced variable degrees of inhibition, with the ethionine group showing the most and the N-2-fluorenylacetamide and thioacetamide groups showing the least; hypertonic NaCl markedly inhibited all groups similarly; and CCl4 induced somewhat variable degrees of inhibition, with the thioacetamide group showing less than the other groups. In a few long-term experiments where hepatomas were evaluated in relation to surrounding liver tissue, puromycin administration induced less inhibition in the hepatomas than in the surrounding liver while actinomycin D administration induced similar inhibition in both groups. In general, in all experiments the degree of polyribosomal disaggregation was parallel to that of inhibition of protein synthesis (in vitro). The results reveal that the livers of rats fed purified diets containing selected hepatocarcinogens responsed in a variable manner in regard to protein synthesis (in vitro) and status of polyribosomal aggregation to the acute administration of selected hepatotoxic agents. (Author abstract) (23 Refs)

9. EFFECTS OF PROLONGED ORAL TREATMENT WITH N-FLUOREN-4-YLACETOHYDROXAMIC ACID ON RAT LIVER FINE STRUCTURE.

Flaks B, Yost Y, Flaks A
Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England
Carcinogenesis; 3(1):103-109 1982

Inbred male Leeds strain rats were given a diet containing 0.05% N-fluoren-4-yla cetohydroxamic acid for up to 7 mo. A modified method for the synthesis of this compound is described. Rats were killed at intervals during and after treatment and their liver tissues examined by light and electron microscopy. The treated rats developed a very low incidence of (nonhepatic) tumors and hepatic clear cell foci appeared during the late stages of the experiment. The only significant fine structural changes observed were glycogenosis and alterations in the morphology of the rough endoplasmic reticulum, both of which developed only after prolonged treatment and affected a minority of hepatocytes. These changes are discussed in relation to the fine structural changes elicited by the strongly carcinogenic N-fluoren-2-ylacetamide and the non-carcinogen, N-fluoren-4-ylacetamide. (Author abstract) (29 Refs)

10. ENZYMES OF NORMAL, PREMALIGNANT, AND MALIGNANT COLONIC CELLS.

Balis ME, Higgins PJ, Salser JS, Stemmerman GN, Magee PN, Wattenberg LW
Dept. Cell Metabolism and Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Banbury Rep; 7:129-139 1981

The villus and crypt cells of rat small intestine contained two different forms of adenosine deaminase (AD) and adenine phosphoribosyltransferase (APRT). The APRTs of normal and neoplastic rat colonic mucosa showed similar properties. Normal colonic mucosa showed predominantly one form of AD, but colonic tumors induced by methylazoxymethanol showed two distinct forms. The ADs of human colonic mucosa and colonic cancer were also distinctive. The tumor AD was smaller than that of normal tissue and was also immunologically distinct. In rat colon, ornithine decarboxylase (ODC) activity was about the same as in liver and only 1-2% that of the small intestine. Carcinogens caused a marked increase in the ODC activity of the target tissue: acetylaminofluorene in the liver, and dimethylhydrazine (DMH) in the colon. Thymidine kinase (TK) activity of the intestine was much higher in the fetal rat than in young or mature rats. After the administration of a colonic carcinogen (DMH), the colonic TK activity increased to levels resembling the fetal TK activity. Assays using rabbit antisera demonstrated two types of TK in normal human intestine, representing the flat mucosa and the crypts. A rabbit antibody against TK from human term placenta cross-reacted against cells from a number of tumor types, including abnormal cervical cells in Papanicolaou smears and colon carcinoma cells. This antibody also reacted with skin fibroblasts from patients with familial colonic polyposis. The specificity of the TK antibody for a variety of tumor types was greatly reduced by preabsorbing the rabbit antiserum with normal human colon extracts. (11 Refs)

11. DNA METHYLASE ACTIVITY OF NORMAL LIVER, REGENERATING LIVER, AND A TRANSPLANTABLE HEPATOCELLULAR CARCINOMA.

Walker MS, Becker FF
(c/o Becker) Dept. Pathology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Biochem Biophys; 5(3):169-173 1981

DNA methylase was obtained from regenerating rat liver (RRL) from male ACI animals in which transplantable hepatocellular carcinoma (THC 252) had been induced by exposure to N-2-acetylaminofluorene, from normal rat livers (NRL), and from THC 252 nuclei (THC). The activities of DNA methylase in crude extracts of NRL, RRL, and THC, determined by methylation of denatured Micrococcus luteus DNA, were as follows: NRL less than RRL less than THC. A similar assay with Escherichia coli and calf thymus DNAs, both single- and double-stranded, confirmed that methylase activities of the three tissues remain in the same order regardless of substrate. Methylation saturation studies performed with DNAs from the same three rat tissues showed that THC 252 DNA is hypomethylated, and that the undermethylation does not result from an inability of THC 252 methylases to methylate THC 252 DNA. The results confirm earlier findings obtained by direct analysis of 5-methylcytosine content; chromatin composition or configuration is the most likely explanation for hypomethylation. (25 Refs)

FLUORENAMINES: IN VITRO

12. RAPID RELEASE OF CARCINOGEN-GUANINE ADDUCTS FROM DNA AFTER REACTION WITH N-ACETOXY-2-ACETYLAMINOFLUORENE OR N-BENZOYLOXY-N-METHYL-4-AMINOAZOBENZENE.

Tarpley WG, Miller JA, Miller EC
McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
Carcinogenesis; 3(1):81-88 1982

Reaction of N-benzoyloxy-N-methyl-4-aminoazobenzene (N-benzoyloxy-MAB) or N-acetoxy-N-acetyl-2-aminofluorene (N-acetoxy-AAF), model ultimate aromatic amine or amide carcinogens, with [purine-14C]DNA at pH 7.4 or reaction of N-hydroxy-2-aminofluorene (N-hydroxy-AF) at pH 4.6 resulted in the rapid release of 14C-containing products not precipitable with the DNA. Four such products were obtained on reaction with N-acetoxy-AAF, two with N-hydroxy-AF, and six with N-benzoyloxy-MAB. Depending on the DNA sample used, the total amounts of 14C in these products from the reactions with N-benzoyloxy-MAB or N-acetoxy-AAF ranged from about 5% to as much as 30-40% of the amounts in the N-(deoxyguanosin-8-yl)-MAB or N-(deoxyguanosin-8-yl)-AAF residues in the DNA from the same reaction mixtures. Reactions with N-acetoxy-[acetyl-3H]AAF showed that the two major products retained the amide residue from the N-acetoxy-AAF. when the reactions were carried out with [guanine-(8-3H; 8-14C); adenine-(2,8-3H; 8-14C)]DNA, the two major products formed from N-acetoxy-AAF and four products formed from N-benzoyloxy-MAB had very low 3H:14C ratios; these ratios were those expected for guanine derivatives which had lost the 8-3H. Studies on the major DNA adducts N-(deoxyguanosin-8-yl)-MAB and N-(deoxyguanosin-8-yl)-AAF indicated that the new adducts were not formed from these nucleosides. The data suggest that the two major AAF products and the four MAB adducts studied are guanine derivatives formed by depurination of N-7 substituted adducts in the DNA. (Author abstract) (49 Refs)

13. THE INFLUENCE OF MONOCYTE (ADHERENT CELL) CONTENT IN HUMAN MONONUCLEAR BLOOD CELL POPULATIONS ON THE ESTIMATION OF INDIVIDUAL LEVELS OF N-ACETOXY-2-ACETYLAMINOFLUORENE INDUCED UNSCHEDULED DNA SYNTHESIS.

Pero RW, Sjogren HO
Biochemical and Genetic Ecotoxicology, Wallenberg Lab., Univ. Lund, Box 7031, 220 07 Lund, Sweden
Carcinogenesis; 3(1):39-43 1982

Human mononuclear blood cells were isolated from heparinized blood samples by centrifugation in Isopaque-Ficoll gradients. The isolated mononuclear cells were then subjected to further fractionation according to size by sedimentation at unit gravity. The faster sedimenting cells containing high proportions of monocytes were two-fold greater at carrying out N-acetoxy-2-acetylaminofluorene (NA-AAF) induced unscheduled DNA synthesis (UDS) than were cell fractions containing only lymphocytes. Furthermore, the mononuclear cell populations that adhere to plastic surfaces were shown to be responsible for the increased NA-AAF induced UDS observed for the cells that sediment at a faster rate in a unit gravity gradient. Interindividual fluctuations in NA-AAF induced UDS estimated on mononuclear blood cells could not be explained in terms of fluctuations in adherent cell (monocyte) NA-AAF induced UDS when the general population was examined. These data support the notion that although monocytes have a greater DNA repair synthesis, the variation in monocyte content and/or function encountered in the general population is not great enough to seriously affect interindividual comparisons of NA-AAF induced UDs. (Author abstract) (27 Refs)

14. DETECTION OF CHEMICAL CARCINOGENS BY ASSAY OF UNSCHEDULED DNA SYNTHESIS IN RAT TRACHEAL EPITHELIUM IN SHORT-TERM ORGAN CULTURE.

Ide F, Ishikawa T, Takayama S

Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan

J Cancer Res Clin Oncol; 102(2):115-126 1981

A short-term organ culture of rat tracheal epithelium was used to detect the ability of 53 chemicals to induce UDS. In this system all direct-acting compounds (ultimate or proximate carcinogens) tested induced UDS. Of 24 compounds requiring metabolism (procarcinogens), nine induced UDS, viz, 4NQO, AF-2, BP, DMN, DEN, and NP. Urethane, AAF, and 2,7-AAF induced very slight UDS. 3-Methyl-4NQO for which carcinogenicity data is incomplete was positive in our system. Among the cancer chemotherapeutic agents tested only mitomycin C induced UDS. MC and DMBA, which are known to induce cancer of respiratory organs in experimental animals, and DAB, aflatoxin B1 and Trp-P-1, which are strong carcinogens in the liver, did not induce UDS within 2 hr. With the longer exposure (24 hr), these carcinogens also failed to elicit UDS. All the carcinogens that induce UDS showed clear dose-dependent effects. No non-carcinogens tested induced UDS. These results suggested that this system should be useful for screening environmental chemicals suspected of damaging DNA of the respiratory organ on the basis of organotropic effects of UDS induction in cultured rat tracheal epithelium. (Author abstract) (54 Refs)

15. THE ACTIVITY OF 4CMB IN THE BHK CELL-TRANSFORMATION ASSAY.

Styles J, Penman S

Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England

Mutat Res; 100(1-4):227-228 1982

The baby hamster kidney (BHK) transformation assay was used to study carcinogenic potential of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 2-acetylaminofluorene (2AAF). A positive response was obtained with 4CMB and 2AAF but a negative result was observed with BC. The BHK assay demonstrated that 4CMB is a potent in vitro transforming agent in the absence of S9 mix. BC, a known carcinogen, was negative in the assay, suggesting that 4CMB and BC were tested in a system where the conditions of the test did not reflect those in vivo. (6 Refs)

16. THE EFFECT OF TESTOSTERONE TREATMENT ON THE ABILITY OF FEMALE RAT LIVER S9 TO ACTIVATE AFLATOXIN B1 AND 2-AMINOFLUORENE IN THE AMES/SALMONELLA SYSTEM.

Chernesky P, Jayaraj A, Richardson A

Dept. Chemistry, Illinois State Univ., Normal, IL, 61761

Mutat Res; 103(3-6):267-273 1982

The activation of aflatoxin B1 (AFB1) and 2-aminofluorene (2AF) by liver homogenates (S9) from untreated and testosterone-treated female Fischer F344 rats was compared using the Ames Salmonella (TA98)/microsome assay. Testosterone treatment resulted in a 93% increase in the ability of S9 to convert AFB1 to mutagenic compounds in the Ames test and a 43% increase in the similar activation of 2AF. (21 Refs)

17. AGE-RELATED CHANGES IN MUTAGEN ACTIVATION BY RAT TISSUES.

Robertson IG, Birnbaum LS

(c/o Birnbaum) Environmental Biology Branch, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709

Chem Biol Interact; 38(2):243-252 1982

Age-related changes in drug metabolism of the liver, lung and kidney of adult female Long-Evans rats were determined by measuring changes in mutagen formation. Activafion of aflatoxin B1 (AFB1), 2-aminofluorene (AF) and 2-acetylaminofluorene (AAF) to mutagenic derivatives was assayed using the Ames Salmonella test system. The promutagens were incubated with tissue fractions from rats ranging in age from 2.5 to 25 mo. With all three compounds, hepatic, renal and pulmonary activation was lower in the senescent than in the young adult animals. The largest decrease, however, occurred prior to middle-age, ie before 9-13 mo. In liver and kidney, little change was detectable between the middle-aged and the old (20-25 mo) animals. However, pulmonary metabolism in the oldest animals was slightly higher than in the extracts from the middle-aged rats. The observed decline in mutagen activation may thus be a function of maturation rather than senescence. (Author abstract) (30 Refs)

18. RETINOL (VITAMIN A) AS A MODIFIER OF 2-AMINOFLUORENE AND 2-ACETYL-AMINOFLUORENE MUTAGENESIS IN THE SALMONELLA/MICROSOME ASSAY.

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Toxicology Lab., Natl. Food Admin., Box 622, S-751 26 Uppsala, Sweden

Arch Toxicol; 49(2):169-174 1982

Vitamin A (retinol) has been demonstrated to modify the mutagenic activity of the aromatic amines, 2-aminofluorene (2AF) and 2-acetylaminofluorene (2AAF) when added to the Ames Salmonella/mammalian microsome assay. Low amounts of retinol (2-20 ug/plate) increased the mutagenicity of both 2AF and 2AAF. At higher doses (50-150 ug/plates) the mutagenicity of 2AAF remained unchanged while the mutagenicity of 2AF gradually decreased. The present data do not support the hypothesis that retinol generally acts as an inhibitor of in vitro metabolic activation of procarcinogens. (Author abstract) (16 Refs)

19. STIMULATION OF S-9 FRACTION METABOLISM IN RAT LIVER AND BREAST BY VITAL DYES.

Silva MH, Lee RE, Petrakis NL

Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143

Toxicol Lett; 10(2/3):205-208 1982

Known mutagens metabolized in rat liver and breast supernatant fractions were used in the Ames test to assess metabolizing enzyme induction by vital dyes. The mutagen 2-aminoanthracene (2AA) showed a 70% activity increase with neutral red, an 89% increase with methylene blue, and a 49% increase with trypan blue in treated rat liver fractions. The lowest and greatest increase in mutagenic activity with liver fractions was seen with 6-aminochrysene and diaminofluorene, respectively. An activity increase in treated breast fractions was found only with 2AA. Liver tissue was more readily induced than mammary glands of midpregnant rats. (11 Refs)

20. EVIDENCE FOR A CYTOCHROME P-420 CATALYZED MECHANISM OF ACTIVATION OF N-HYDROXY-2-ACETYLAMINOFLUORENE.

Reigh DL, Floyd RA
Dept. Math/Science, Univ. Science and Arts of Oklahoma, Chickasha, OK, 73018
Cancer Biochem Biophys; 5(4):213-217 1981

Cytochromes P-450 and P-420 were solubilized from microsomes from perfused livers of phenobarbital-treated male rats. Electron spin resonance spectroscopy revealed the formation of a nitroxyl radical intermediate in the reaction activating N-hydroxy-2-acetylaminofluorene (N-OH-AAF) in the presence of linoleic acid hydroperoxide. The studies suggest the involvement of the P-450 system in conversion of N-OH-AAF to N-acetoxy-2-acetylaminofluorene and 2-nitrosofluorene, and confirm that the P-420 system, whether naturally occurring in microsomes or induced to form P-420 spin forms, is capable of catalyzing peroxidative type reactions. (18 Refs)

21. THE EFFECTS OF NITROUS ACID ON THE MUTAGENICITY OF TWO COAL LIQUIDS AND THEIR GENETICALLY ACTIVE CHEMICAL FRACTIONS.

Pelroy RA, Stewart DL
Pacific Northwest Lab., Richland, WA, 99352
Mutat Res; 90(4):297-308 1981

The mutagenicity of solvent refined coal (SRC) distillates and distillate fractions was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. Chemicals tested included SRC-II heavy distillate (HD), SRC-I process solvent (PS), basic tar and neutral tar fractions of HD and PS, and samples of these chemicals that had been treated with either HCl or HNO2. SRC samples dissolved in dimethylsulfoxide or emulsified in HCl medium contained mutagens that required activation by S9 enzymes. Treatment of SRC samples with HNO2 reduced the observed mutagenicity. Mutagens detected after HNO2 treatment were direct acting; mutagenicity of the substances was apparently decreased by S9 enzymes. HCl did not decrease the mutagenicity of SRC samples. In the absence of S9 enzymes, mutagenicity of SRC compounds was reduced by 73% for PS, 80% for PS basic and neutral tars, and at least 90% for other SRC samples, compared with untreated samples. In the presence of S9 enzymes all HNO2-treated samples showed less than 10% of the mutagenicity of untreated samples. HNO2 treatment did not reduce mutagenicity of the nonprimary aromatic amine polycyclic compounds phenanthridine, dimethylbenzacridine, benzo[a]pyrene, and 2-acetylaminofluorene. Results suggest that primary aromatic amines are the most important contributors to mutagenicity of SRC distillates in the Ames assay system. (21 Refs)

22. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein E
Gulf South Res. Inst., New Orleans, LA
Methods for the Recovery of Organic Carcinogens from Water. Available from National Technical Information Service, Springfield, VA, as PB81-209694:, 41 pp., 1981.

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater and in yields of 40% or more from lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. More polar carcinogens such as dimethylnitrosamine were not effectively recovered on XAD-2 columns. Since XAD-2 binding would not be selective for carcinogens, the authors investigated methods which might bind carcinogens selectively from a mixture of organic compounds. We tested the ability of the above carcinogens to bind to nucleic acid using direct binding, equilibrium dialysis, nuclei binding, and binding to DNA-cellulose. Radio-labeled carcinogens were used to quantify the amount bound. Either rat liver nuclei (0.1 mg DNA) or DNA-cellulose (1 mg DNA) bound 18% of the acetylaminofluorene and up to 66% of the dieldrin from solutions containing 150 to 280 nmoles of compound. Up to 30% of the benzo(a)pyrene from solutions containing as much as 320 pmoles was bound. Tenfold or lower recoveries were found when direct-binding methods were used. (Author abstract)

OTHER FUSED RING AMINES

23. LIFETIME CARCINOGENICITY STUDY OF 1-AND 2-NAPHTHYLAMINE IN DOGS.

Purchase IF, Kalinowski AE, Ishmael J, Wilson J, Gore CW, Chart IS
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderly Park, Macclesfield, Cheshire, England
Br J Cancer; 44(6):892-901 1981

Groups of male and female beagle dogs were given daily doses of 400 mg of various mixtures of naphthylamines for up to 109 mo. Survivors were killed at 128 mo. A variety of pathologic conditions were diagnosed, but the only effect related to treatment was the induction of bladder neoplasms. All dogs which received pure 2-naphthylamine developed transitional-cell carcinomas of the bladder within 34 mo. Two of eight dogs receiving 6% 2-naphthylamine in 1-naphthylamine developed early carcinoma and two of eight dogs receiving 0.5% 2-naphthylamine in 1-naphthylamine developed hemangioma of the bladder. Some of the dogs receiving 1-naphthylamine (total dose 950 g) and the controls had focal cystitis or hyperplasia, but no neoplasia of the bladder. These results confirm the carcinogenicity of 2-naphthylamine to dogs. No carcinogenic effect of 1-naphthylamine was observed, indicating that it is at least 200x less potent as a carcinogen than 2-naphthylamine. The incidence of bladder cancer in dogs fed mixtures of both naphthylamines explains why previous experimental and epidemiological studies of impure 1-naphthylamine have revealed carcinogenicity. (Author abstract) (22 Refs)

24. BIOTRANSFORMATION OF N-PHENYL-BETA-NAPHTHYLAMINE TO BETA-NAPHTHYLAMINE IN A LABORATORY SLUDGE SYSTEM.

Ku Y, Alvarez G
Div. Chemical Technology, Bureau of Foods, Food and Drug Admin., Washington, DC, 20204
Chemosphere; 11(1):41-46 1982

Activated sludge was obtained from a treatment plant in Lorton, Virginia and used to determine whether beta-naphthylamine (BNA), a potent bladder carcinogen in humans, is produced from N-phenyl-beta-naphthylamine (PBNA) by sludge microorganisms under laboratory conditions. PBNA was shown to undergo biotransformation to BNA in an aerobic laboratory sewage system. Thus if PBNA enters sewage treatment plants, BNA will likely be formed and released to the aquatic environment. (11 Refs)

25. FACTORS THAT AFFECT INTESTINAL BACTERIAL ACTIVITY: IMPLICATIONS FOR COLON CARCINOGENESIS.

Goldin BR, Lombardi P, Mayhew J, Gorbach SL, Tannenbaum SR, Wilkins TD, Reddy BS, Goldman P, Hill DH, Montesano R, Magee PN, Strobel HW
Dept. Medicine, Infectious Disease Services, Tufts-New England Medical Center, Boston, MA, 02111
Banbury Rep; 7:41-57 1981

Several experiments in male Fischer rats showed significant dietary effect on fecal beta-glucuronidase (B-Gase), nitroreductase (NRase), and azoreductase (AzRase) activities. Diets containing high levels of beef protein or beef fat were associated with a significant increase in these enzymes. The metabolic conversion of 2-nitronaphthalene (2-NN) or 2-naphthylamine-beta-D-glucuronide to 2-naphthylamine (an index of NRase activity) was significantly higher in beef-fed rats than in grain-fed controls. Dietary supplementation with Lactobacillus acidophilus, tetracycline, or erythromycin reduced fecal enzyme activities in the meat-fed rats to those in controls. The mutagenicity of 2-NN in a NRase-negative Salmonella strain was enhanced in the presence of liver microsomes only by a fecal extract containing NRase activity. Significant dietary effects on fecal enzyme activity were also observed in American adults (20-35 yr old). Lacto-vegetarians and strict vegetarians showed lower fecal B-Gase, NRase, AzRase, and 7-alpha-dehydroxylase activities than omnivores. No major differences were noted between the two vegetarian groups. Dietary supplementation with Lactobacillus caused decreases in fecal B-Gase, NRase, and AzRase activities in omnivores. The enzyme activities returned to baseline values after the supplementation was stopped. The high-animal protein and high-animal fat diets, which are associated with an increased risk of colorectal cancer, caused an increase in bacterial enzymes capable of generating carcinogens in the colon in the rats. The similar association between dietary habits and fecal enzyme activities in humans may provide a partial explanation for the strong positive correlation between daily beef and fat consumption and the incidence of colorectal cancer. (11 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

26. INDUCTION OF DRUG-METABOLIZING ENZYMES IN THE RAT LIVER BY 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE.

Hino O, Nemoto N, Nagao M, Kosugi A, Kitagawa T
Dept. Pathology, Cancer Inst., Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Cancer Lett; 15(2):131-136 1982

The hepatic drug metabolizing system was examined in male Donryu rats fed a normal diet or a diet containing 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB: 1-600 ppm) for 1 or 3 wk. Microsomal cytochrome P-450 content was not affected after 1 wk of 3'-Me-DAB administration but was significantly higher after 3 wk of treatment with 10, 20, or 600 ppm of the carcinogen. Liver S-9 fraction from rats treated with 3'-Me-DAB (20 or 300 ppm, 3 wk) produced a significant, dose-dependent increase in number of 3-methylcholanthrene-induced revertants in the Ames test; when 3-amino-1-methyl-5H-pyrido[4,3-b]indole was used as the mutagen, a significant increase in the number of revertants was induced by S-9 from rats treated with the higher dose. The results indicate that dietary 3'-Me-DAB induces cytochrome P-450 in the liver and that the increase in drug metabolizing capacity can be detected efficiently by the Ames Salmonella test. (25 Refs)

27. MUTAGENICITY OF AZO DYES IN THE SALMONELLA/ACTIVATION TEST.

Robertson JA, Harris WJ, McGregor DB
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Carcinogenesis; 3(1):21-25 1982

The detection of certain bis-azo biphenyl dyes (Trypan blue, Evans blue and Congo red) by a modification of the standard Ames test protocol is reported. Detection of a mutagenic response required both the inclusion of FMN in S-9 mix and use of a static pre-incubation step prior to addition of top-agar and pouring in the usual manner. Evidence is presented to substantiate the proposal that use of this protocol provides optimal conditions for the two stages of activation required for the production of mutagenic metabolites from these dyes. These are (i) initial flavin-mediated (hepatic) azo reduction resulting in the formation of proximate mutagenic metabolites followed by (ii) the oxidative metabolism by S-9 resulting in the formation of ultimately mutagenic products. (Author abstract) (16 Refs)

HETEROCYCLIC AMINES

28. MUTAGENICITY OF AMINOCARBAZOLES AND NITROCARBAZOLES.

LaVoie EJ, Govil A, Briggs G, Hoffmann D
Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Mutat Res; 90(4):337-344 1981

Mutagenic activity (MA) of the C-substituted nitro and amino derivatives of carbazole was studied in Salmonella typhimurium TA98 and TA100 using the Ames assay. As a metabolic activation system, S9 preparations were obtained from rats treated with Aroclor. Bacterial cultures were exposed to nitrocarbazoles (1, 2, 5, 10, 25, 50, 100, or 200 ug/plate) or aminocarbazoles (5, 10, 25, 50, 100, or 200 ug/plate). In the absence of S9, 2-nitrocarbazole (2NC) and 3-nitrocarbazole (3NC) were mutagenic towards TA98 cultures, while 1-nitrocarbazole (1NC) and 4-nitrocarbazole (4NC) were not. 2NC had MA similar to that of 2-nitrofluorene. In the presence of S9 the MA of 2NC and 3NC was reduced, 4NC showed weak MA, and 1NC remained inactive towards T98. 1NC and 3NC showed no MA towards TA100 with or without S9. 4NC showed MA towards TA100 with or without S9. 2NC showed weak MA with S9. All aminocarbazoles showed greater MA with S9 than without S9. 1-Aminocarbazole was inactive towards both TA98 and TA100. MA of 2-aminocarbazole was greater than that of 2-aminofluorene (2AF) without S9 and less than that of 2AF with S9. 3-Aminocarbazole showed moderate MA towards TA98 with S9 but no MA towards TA100. 4-Aminocarbazole showed MA towards TA100 but only marginal MA towards TA98. Because none of the test compounds showed MA towards the exclusive base pair tester strain TA1535, specificity in base pair or frame shift mechanism of action between isomers could not be confirmed. (15 Refs)

29. ANTICHOLINESTERASE ACTIVITY OF THE UNSYMMETRIC BISQUATERNARY 6-AMINOQUINOLINE SALT NSC-176319.

Hacker MP, Braddock J, Unwin S
Dept. Pharmacology, Univ. Vermont Sch. Medicine, Burlington, VT, 05405
Biochem Pharmacol; 31(3):301-304 1982

The anticholinesterase activity of the unsymmetric bisquaternary 6-aminoquinoline salt NSC-176319 (QB) was studied in vitro. QB proved to be a noncompetitive inhibitor of both acetylcholinesterase (or true cholinesterase) and butyrylcholinesterase (or pseudocholinesterase) having a KI = 0.5 x 10(-6) M for acetylcholinesterase and 1.5 x 10(-6) M for butyrylcholinesterase. Further, QB inhibited esterase activity of murine plasma in a noncompetitive manner (KI = 4.2 x 10(-6) M). The inhibition was instantaneous in onset and did not diminish with prolonged incubation of the drug and enzyme. All mice treated intravenously with 2 mg QB/kg died within 5 min. Prior to death, mice developed severe parasympathomimetic effects and convulsions. Although the parasympathomimetic effects were diminished by atropine sulfate pretreatment, death could only be prevented by barbiturate anesthesia. (Author abstract) (13 Refs)

30. NEOPLASTIC TRANSFORMATION OF HUMAN DIPLOID FIBROBLASTS TREATED WITH CHEMICAL CARCINOGENS AND CO-60 GAMMA-RAYS.

Namba M, Nishitani K, Fukushima F, Kimoto T, Utsunomiya J, Hayflick L
Dept. Pathology, Kawasaki Medical Sch., Matsushima 577, Kurashiki 701-01, Japan
Gann Monogr Cancer Res; 27:221-230 1982

Transformation of four strains of normal human fibroblasts with repeated treatment with 4-nitroquinoline 1-oxide (4NQO) and two strains with 60Co gamma-rays is reported. Single treatment with those agents had no such effect. A total of 256 experiments were conducted, 116 with 4NQO and 49 with 60Co gamma rays. The transformed cell lines had the following features; epithelial-like morphology, unlimited growth potential, abnormal karyotypes (heteroploid), increased saturation density, reduced growth inhibition by theophylline, increased lactate dehydrogenase isozyme B(H)/A(M) ratio, no large external transformation sensitive protein, elevated colony formation in soft agar, and a low serum requirement for growth. When unlimited growth and abnormal karyotypes are present, neoplastic transformation in human cells is indicated. Criteria of the morphology of transformed colonies were defined. Advantages and disadvantages of using normal human fibroblasts for transformation studies were discussed. Future considerations for the use of normal human fibroblasts for transformation studies were proposed. (21 Refs)

31. CHEMICAL CARCINOGENS TRANSFORM BHK CELLS BY INDUCING A RECESSIVE MUTATION.

Bouck N, Di Mayorca G
Dept. Microbiology/Immunology, Northwestern Univ., Chicago, IL, 60611
Mol Cell Biol; 2(2):97-105 1982

Mechanisms of transformation (TF) by chemical carcinogens were studied in the baby hamster kidney cell line BHK-21 clone 13. Tumorigenic transformed cell lines were derived from BHK cells by exposure to papovavirus (PV), dimethylnitrosamine (DMN), nitrosomethylurea (NMU), or 4-nitroquinoline-N-oxide (4-NQO) or by spontaneous transformation. NMU or 4-NQO produced TF and mutations to 6-thioguanine-resistance (6-TGR) or ouabain-resistance (OR) in a dose-related fashion. Parallel dose-response curves for TF, 6-TGR, and OR suggested that TF and mutation occurred by similar mechanisms. Two frame-shift mutagens, ICR-170 and ICR-191, had dose-response curves for survival and TF that were identical. Both compounds produced temperature-restriction mutations in inverse proportion to frame-shift mutations. Fusion of transformed cells with isogeneic normal cells showed that TF induced by PV behaved as a genetic dominant, but spontaneous or chemically induced TF behaved as a genetic recessive. These genetic patterns were exhibited soon after fusion and also after establishment of hybrid clones. All hybrids were nearly tetraploid. Hybrids showed segregation of TF; transformed phenotype was reexpressed in most cases in the form characteristic of the original transformed parent. Results indicate that chemical carcinogenesis in BHK cells involves induction of a recessive mutation as part of a multistage process. (58 Refs)

32. CELL POPULATION KINETICS IN RAT PALATAL EPITHELIUM TREATED WITH THE CARCINOGEN 4-NITROQUINOLINE N-OXIDE (4NQO).

Fisker AV, Karring T
Dept. Oral Pathology, Royal Dental Coll., Vennelyst Blvd., DK-8000 Arhus C, Denmark
J Oral Pathol; 10(6):408-416 1981

Cell population kinetics was investigated in rat palatal epithelium treated with a 0.5% soln of 4-nitroquinoline N-oxide (4NQO) in propylene glycol 3x/wk for 2 wk or 2 mo. Ulcerations were observed in the palatal mucosa 3 days after the first application; all healed after 1 wk. Numerous papillary excrescences were observed on the mucosal surface 1-2 wk after cessation of the 2-wk treatment. The epithelium was hyperplastic; this gradually decreased. No carcinoma or dysplasia was observed. After 2-mo treatment, papillary excrescences were larger than in animals treated for 2 wk. A severely folded hyperplastic epithelium was seen. Carcinomas at the intermolar area developed in three animals. After termination of 4NQO application, the mitotic rates, mitotic counts, and mitotic durations of the experimental animals in both groups were not significantly different from those of the control animals. Thus, under the conditions used, 4NQO did not induce irreversible changes in cell population kinetics of the palatal epithelium. These data indicate that an animal model system resulting in a high incidence of carcinomas should be used when studying cell population kinetics and that stress factors which might induce arrest of mitosis should be avoided. (23 Refs)

33. EXCISION REPAIR OF DNA DAMAGE PRODUCED BY 4-NITROQUINOLINE 1-OXIDE IN CULTURED MAMMALIAN CELLS: ITS RELATION TO CARCINOGENESIS.

Ikenaga M
Dept. Fundamental Radiology, Osaka Univ. Faculty Medicine, Nakanoshima 4-3-57, Kita-ku, Osaka 530, Japan
Gann Monogr Cancer Res; 27:21-32 1982

Molecular mechanisms of repair of DNA lesions induced by 4-nitroquinoline 1-oxide (4NQO) in cultured mammalian cells were studied. In UV-irradiated xeroderma pigmentosum (XP) cells, the level of 4NQO-induced unscheduled DNA synthesis (UDS) was lowest in complementation group A, and increased in groups B, C, D, and E in order. In Cockayne's syndrome cells, normal levels of UDS after UV or 4NQO treatment were found. Epidermodysplasia verruciformis cells showed a slightly reduced level of UDS after UV irradiation and were highly sensitive to 4NQO. Variable responses to 4NQO were observed in cells of ataxia telangiectasia. The major 4NQO lesions produced in DNA of cultured human cells were a stable major 4NQO-guanine adduct, a stable minor 4NQO-guanine adduct, a stable major 4NQO-adenine adduct, and an unstable major 4NQO-guanidine adduct that releases 4-aminoquinoline 1-oxide upon hydrolysis. The excision repair of 4NQO-purine adducts from DNA of normal human cells and its absence in XP cells was demonstrated. Studies with mouse cells demonstrated that 4NQO-purine adducts are the major cause of 4NQO carcinogenesis. These findings are discussed with respect to excision repair, which may be important in chemical carcinogenesis. (49 Refs)

34. EXCISION AND CROSSLINK REPAIR OF DNA AND SISTER CHROMATID EXCHANGES IN CULTURED HUMAN FIBROBLASTS WITH DIFFERENT REPAIR CAPACITIES.

Fujiwara Y, Kano Y, Paul P, Goto K, Yamamoto K, Miyazaki N
Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-5-1, Chuo-ku, Kobe 650, Japan
Gann Monogr Cancer Res; 27:33-44 1982

The relationship between sister chromatid exchange (SCE) induction and DNA repair was studied by evaluating the role of UV excision repair. The roles of interstrand crosslinking and repair in the induction of SCE in fibroblasts of xeroderma pigmentosum (XP) complementation groups (A to G and a variant group), Cockayne's syndrome (CS), and Fanconi's anemia (FA) with different repair capacities and predispositions to malignancies were studied. Killing sensitivities of the three types of cells to UV, 4-nitroquinoline-1-oxide (4NQO), and monofunctional decarbamoyl mitomycin C (DCMC) are reported. The XP groups were deficient in the initial steps of dimer excision repair in the order of A = G greater than C greater than D greater than D = F greater than variant. The extent of dimer-repair deficiency strictly determined the killing sensitivity of XP cells. Studies of the susceptibilities of XP and CS cells to SCEs induced by mutagens demonstrated that in the most defective XP group-A cells, the SCE induction rate by UV, 4NQO, and DCMC was a 3-5-fold higher than in normal cells. FA cells were approx 1.7x more sensitive to SCE induction by MC than normal cells and the SCE rate induced by DCMC was the same as that of normal cells. In XP cells, a sixfold higher SCE rate was observed after DCMC, and only a slightly higher SCE rate was observed after MC. Thus, part of cross-link damage may yield SCE. Caffeine synergistically increased UV-induced SCEs, but not UV-induced mutations in V79 cells, thus, dissociated SCE from mutation. (21 Refs)

35. ISOLATION AND IDENTIFICATION OF THE ALKALOIDS FROM ANCISTROCLADUS TECTORIUS.

Chen Z, Wang B, Qin K, Zhang B, Su Q, Lin Q
Shanghai Inst. Materia Medica, Chinese Acad. Sciences, Shanghai, People's Republic of China
Yaoxue Xuebao; 16(7):519-523 1981

During the screening of plants for antitumor constituents, the crude alkaloid extracted from twigs and stems of Ancistrocladus tectorius with the aid of 95% ethanol was found to have an inhibitory effect on Walker 256 tumor in rats. To determine the active component, the free bases present in the crude alkaloid preparation were extracted with ether, the ether was removed, and the preparation was then chromatographed on an alkaline silica gel column, using chloroform: methanol (30:1 and 20:1) as the eluant; three crystalline fractions were thereby obtained. Recrystallization yielded pure crystalline products I, II, and III. Using standard chemical and physical methods (elemental analysis; mass spectrometry; IR, UV, and NMR spectroscopy), I and II were identified as ancistrocladine and hamatine, respectively (both known alkaloids), while III was determined to be a new alkaloid, 5-(4,5-dimethoxy-2-methylnaphthyl)-1,2,3,4-tetrahydro 6-hydroxy-8-methoxy-1,3-dimethylisoquinoline, and was named ancistrocline. NMR spectral data showed the 1-and 3-methyl groups in ancistrocline to be equatorial. The antitumor activities of the total alkaloids and of the fractions I and II were weak against murine S-180 and Ehrlich ascites tumors. (7 Refs) (In CHI)

REVIEWS AND OTHER RELATED STUDIES

36. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.

Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

A significant portion of the incidence of human urinary bladder cancer can be attributed to occupational and cultural (tobacco smoking) situations associated with exposures to various arylamines, many of which represent established human carcinogens. A brief historical overview of research in bladder cancer causality indicates that the identification of causal agents and causal mechanism has been approached and rests upon information gathered at the organismal (geographical/historical), cellular, and molecular levels of biologic organization. This viewpoint speaks of a natural evolution within the biomedical sciences; a natural evolution from descriptive approaches to mechanistic approaches; and a natural evolution from more or less independent discipline-oriented approaches to hierarchically organized multidisciplinary approaches. Available information relevant to bladder cancer causality can be readily integrated into general conceptual frameworks to yield a hierarchial view of the natural history of urinary bladder cancer, a view consistent with contemporary natural systems and information theory and perhaps relevant also to other chemically induced epithelial cancers. Such frameworks are useful in appreciating the spatial and temporal boundaries and interrelationships in causality and the conceptual interrelationships within the biomedical sciences. Recent approaches in molecular epidemiology and the assessment of relative individual susceptibility to bladder cancer indicate that such frameworks are useful in forming hypotheses. (Author abstract) (62 Refs)

37. THE KIDNEYS: COMPLEX CLEANSING UNITS.

Willis J
FDA Consumer, Rockville, MD, 20857
FDA Consum; 15(10):12-15 1982

Kidney anatomy and physiology, effects of several hormones (vasopressin, aldosterone the renin-angiotensin-aldosterone system) and drugs on kidney reabsorption and secretion, components of urine which indicate diseases, common symptomatology of several kidney diseases, cancer of the urinary system, dialysis, and renal transplantation are discussed. Symptomatology of kidney tumors (which may be quite large before they are detected) may be microscopic blood in the urine during the early stages of the tumor. The most common sign of bladder cancer is gross hematuria. Bladder tumors occur 4x more often in men than in women and usually occur after age 50. Incidence of bladder cancer is higher than average in people who work with aniline dyes, benzene, and naphthalene. Early treatment of bladder cancer consists of radiation or local surgical removal; later, complete removal of the bladder is necessary. (no Refs)

38. CARCINOGENIC EFFECTS OF COAL-CONVERSION MATERIALS.

Renne RA, Smith LG
Batelle Pacific Northwest Lab., Richland, WA
Carcinogenic Effects of Coal-Conversion Materials. Available from National Technical Information Service, Springfield, VA, as DE81028108:, 29 pp., 1981.

Tremendous expense and extensive time commitments are required for in vivo mammalian carcinogenesis tests. Regulatory agencies may not be completely satisfied without some repetition of the toxicity testing with the final product from the commercial plant. Nevertheless, I think the work that we are doing on these materials from the pilot and demo plants is valuable. We are attempting to determine the correlation between mutagenesis and carcinogenesis data on complex mixtures such as these synfuel materials. The heavy distillate that we are working with was highly mutagenic compared with the other materials tested in the Ames system; it was also highly carcinogenic in our mouse skin-painting assay. when we tested the fractions, we had somewhat different results from those of the mutagenesis assays: the basic fraction of the heavy distillate was highly mutagenic, but, at least now, it does not appear to be highly active in our mouse carcinogenesis assay. However, the basic tar and the neutral tar skin carcinogenesis data correlate fairly well with the mutagenesis data. The second point I would like to make is to emphasize the need for caution against depending heavily on equating PNA content with carcinogenic activity. I would like to point out that our data indicate that PNAs are not the only chemical group with which we should be concerned. We should also monitor for primary aromatic amines. Due to the concern inhalation of synfuels, we have begun inhalation studies on some of the SRC materials. (Author abstract)

39. COMPARATIVE EVALUATION OF DIFFERENT PAIRS OF DNA REPAIR-DEFICIENT AND DNA REPAIR-PROFICIENT BACTERIAL TESTER STRAINS FOR RAPID DETECTION OF CHEMICAL MUTAGENS AND CARCINOGENS.

Suter W, Jaeger I
Preclinical Res. Dept. Toxicology Unit, Sandoz Ltd., Basle, Switzerland
Mutat Res; 97(1):1-18 1982

Carcinogenic and noncarcinogenic compounds, including antibiotics, polycyclic aromatics, aromatic amines, alkyl halides, esters, epoxide carbamates and related compounds, nitroaromatics and heterocyclics, nitroso compounds, hydrazine compounds, azo compounds, and other bioactive agents, were tested for mutagenicity with the agar incorporation test (AT) and the spot test (ST). Two paired (DNA repair proficient/repair deficient) Bacillus subtilis systems, H17/M45 and HLL3g/HJ-15, were used, and the repair-proficient Escherichia coli A1157 strain was paired with the repair-deficient strains JC2921, JC2926, JC5519 , and JC5547. Results were compared with reported carcinogenicity and/or Ames test mutagenicity, or in some cases with Ames Salmonella (TA1535, TA1537, TA1538, TA98, TA100) assays reported here for the first time. E coli systems yielded a high number of 'no result' findings as well as many false-positive outcomes. B subtilis systems were generally reliable indicators of carcinogenicity, especially if both AT and ST were used. The bacterial DNA-repair tests agreed more often with the Ames test than with carcinogenicity results. When both pairs of B subtilis strains were combined with the Ames assay, excess false-positives did not appear, whereas the number of false-negative findings with carcinogens was reduced. The slightly increased probability of uncovering a suspected carcinogen does not seem to justify inclusion of the extra tests in a battery, except when working with chemicals of classes in which the Ames test is known to be less sensitive. (59 Refs)

40. POTENTIAL IDENTIFICATION OF CHEMICAL CARCINOGENS IN A VIRAL TRANSFORMATION SYSTEM.

Wilson WW, Khoobyarian N

(c/o Khoobyarian) Dept. Microbiology and Immunology, Sch. Basic Medical Sciences, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680

Chem Biol Interact; 38(2):253-259 1982

Chemical carcinogens from several diverse chemical classes ie; aromatic amines, polycyclic hydrocarbons, nitrosamines, hormonal derivatives, metals and direct alkylating agents cause a 6.2-60.5-fold increase in the frequency of murine sarcoma virus (MSV)-induced transformation in a normal rat kidney (NRK) cell system. Exogenous metabolic activation with a rat liver S-9 homogenate is required for expression of this activity by procarcinogens. Non-carcinogenic analogs of these compounds fail to cause significant increases in the transformation frequency either with or without prior metabolic activation. Iododeoxyuridine, a mutagen also does not cause enhancement of transformation. This system may serve as the basis for a rapid and quantifiable means of identifying chemical carcinogens while introducing a new model for the understanding of the interactions between oncornaviruses and chemical carcinogens. (Author abstract) (14 Refs)

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Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

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Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
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ANILINES AND EXTENDED ANILINES

1. BINDING OF 3,3'-DICHLOROBENZIDINE TO DNA AND POLYRIBONUCLEOTIDES IN VITRO.

Bratcher SC, Sikka HC
Life Sciences Div., Syracuse Res. Corporation, Syracuse, NY
Chem Biol Interact; 38(3):369-375 1982

Covalent binding of 3,3'-dichlorobenzidine (DCB) to calf thymus DNA and some polyribonucleotides in vitro was examined both in the presence and absence of rat liver S-9 fraction to determine the ability to interact directly with cellular macromolecules. DCB reacted with DNA in vitro with or without the S-9 fraction; in the presence of S-9 fraction, the degree of binding was considerably greater. Non-enzymatic binding of DCB increased with time of incubation up to 5 hr. Enzymatic and non-enzymatic bindin g were dependent on concentration of DCB and incubation mixture. No non-specific absorption seemed to be involved. Greater binding of DCB to DNA in the presence of S-9 suggested the formation of more reactive metabolites which bound to DNA. 7,8-benzoflavone (7,8-BF), a monooxygenase system inhibitor, had no effect on the binding of DCB in the absence of S-9 mix. DCB binding to DNA

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through S-9 activation was significantly inhibited by 7,8-BF. The affinity of DCB to various purines and pyrimidines was investigated by incubating different single-sequence polyribonucleotides with DCB. DCB reacted best with poly(G) with or without S-9, although some binding was observed with poly(A), poly(U), poly(C), and poly(I) in the presence of S-9. One molecule of DCB bound 44,000 nucleotides in calf thymus DNA and 13,000 nucleotides in poly(G) in the presence of S-9. The results indicated that DCB binds covalently to DNA and polyribonucleotides via both direct interaction of the parent compound and reactive metabolites generated in the presence of rat liver S-9 fraction. (30 Refs)

2. SKIN ABSORPTION OF ANILINE FROM AQUEOUS SOLUTIONS IN MAN.

Baranowska-Dutkiewicz B
Inst. Chemistry and Physics, Univ. Medical Sch. Silesia, ul. Jagiellonska 4, 41-2000 Sosnowiec, Poland
Toxicol Lett; 10(4):367-372 1982

The rate of aniline skin absorption from diluted aqueous soln was determined by p-aminophenol excretion. The absorption rate increased with increasing concentration of aniline and declined with the duration of exposure. Two-fold increases of aniline concentration in water soln caused about a four-fold increase in the rate of skin absorption. The observed difference in amounts of p-aminophenol excreted and aniline absorbed were not significant. Aniline or aniline soln could present a risk as an industrial poison. (18 Refs)

FLUORENAMINES: IN VIVO

3. INDUCTION OF GAMMAGLUTAMYLTRANSPEPTIDASE-POSITIVE ALTERED HEPATOCYTIC LESIONS BY COMBINATION OF TRANSPLACENTAL-INITIATION AND POSTNATAL-SELECTION.

Ogawa K, Yokokawa K, Tomoyori T, Onoe T
Dept. Pathology, Sapporo Medical Coll., Sapporo 060, Japan
Int J Cancer; 29(3):333-336 1982

The purpose of this study was to induce in postnatal life the selective growth of altered hepatocytic populations which had been induced in utero by various chemicals. Pregnant rats of a Wistar strain were given a single dose of various chemical carcinogens on the 18th gestational day. From 2 mo postpartum, both the mothers and offspring were given a diet containing 2-acetylaminofluorene (2-AAF) at a concentration of 0.02% for 2 wk. Then, at the end of the 1st wk after the 2-AAF feeding, a two-thirds partial hepatectomy was performed. All the animals were killed 1 wk after the partial hepatectomy and were examined for the incidence of gamma-glutamyltranspeptidase (GGT)-positive altered hepatocytic foci in the liver. The transplacental administration of not only a hepatic carcinogen, diethylnitrosamine (DEN) but also 7,12-dimethylbenzanthracene (DMBA), which does not usually produce hepatocellular carcinomas in adult rats, induced GGT-positive altered hepatocytes in the liver of the offspring. These hepatocytes grew into grossly visible hyperplastic nodules within a wk after the two-thirds partial hepatectomy. The possible applicability of the transplacental initiation-postnatal selection model for the short-term assay of transplacental carcinogenicity is discussed. (Author abstract) (21 Refs)

4. DECREASED ACTIVITIES OF GLYCINE AND GUANIDINOACETATE METHYLTRANSFERASES AND INCREASED LEVELS OF CREATINE IN TUMOR CELLS.

Yanokura M, Tsukada K
Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Biochem Biophys Res Commun; 104(4):1464-1469 1982

Activities of glycine methyltransferase and guanidinoacetate methyltransferase (GuM) were measured in various tissues of rats and in hepatoma of rat induced by N-2-fluorenylacetamide. Observation over a period of 8 mo showed a marked decrease of the enzymes in tumor tissue. At the same time, creatine levels in tumor increased significantly, even when GuM was not detected. (23 Refs)

5. FORMATION AND REMOVAL OF (GUAN-8-YL)-DNA-2-ACETYLAMINOFLUORENE ADDUCTS IN LIVER AND KIDNEY OF MALE RATS GIVEN DIETARY 2-ACETYLAMINOFLUORENE.

Poirier MC, True B, Laishes BA
NIH, Building 37, Room 3A19, Bethesda, MD, 21205
Cancer Res; 42(4):1317-1321 1982

Radioimmunoassay has been used to measure acetylated and deacetylated deoxyguanosine C-8 DNA adducts of 2-acetylaminofluorene in liver and kidney DNA of male Wistar-Furth rats fed a dietary regimen of 0.02 or 0.04% 2-acetylaminofluorene. When adduct formation was monitored during continuous feeding up to 60 days, substantial levels of binding (80 fmol/ug DNA) were observed in liver by 1 day, and maximum steady-state values averaging 230 fmol/ug DNA were reached by 30 days. Initially, during the continuous feeding, about 80% of the total C-8 adducts were deacetylated [N-deoxyguanosin(8-yl)aminofluorene], and this proportion increased to about 97% by 15 and 30 days of administration of 0.04 and 0.02% 2-acetylaminofluorene diets, respectively. Levels of C-8 adducts bound to kidney DNA in the same animals averaged 10 to 15% of the liver values with greater than or equal to 80% of these adducts in the deacetylated form. In separate experiments, rats were exposed to 2-acetylaminófluorene for 3, 7, 28, and 112 days; the carcinogen-containing diet was discontinued; and C-8 adducts were monitored during 1, 7, and 28 days of feeding control diet. At both carcinogen doses, after dietary administration for 3 or 7 days, there was a rapid decrease in liver C-8 adducts so that, after 28 days on control diet, 65 to 90% of the original adducts were no longer present in the DNA. In contrast, in animals fed 0.02% 2-acetylaminofluorescene for 28 days, there were high levels (70 to 100% of the original C-8 adduct) remaining on the DNA at the end of 28 days on control diet. This apparent loss in capacity for removal of C-8 adducts is discussed in relation to biological and biochemical changes induced in the rat liver during 2-acetylaminofluorene hepatocarcinogenesis. (Author abstract) (26 Refs)

6. PERSISTANCE OF DNA ADDUCTS IN RAT LIVER AND KIDNEY AFTER MULTIPLE DOSES OF THE CARCINOGEN N-HYDROXY-2-ACETYLAMINOFLUORENE.

Beland FA, Dooley KL, Jackson CD
Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079
Cancer Res; 42(4):1348-1354 1982

Male and female Sprague-Dawley rats were treated by gastric intubation either 1, 2, 3, or 4 times at biweekly intervals with 10-mg/kg doses of the hepatocarcinogen N-[ring-3H]-hydroxy-2-acetylaminofluorene. Then either 1 or 14 days following the last treatment, the concentrations of 2-aminofluorene and 2-acetylaminofluorene adducts in liver and kidney DNA were established. 2-Acetylaminofluorene adducts were found in male rat liver DNA only. The C-8-acetylated adduct, N-(deoxyguanosin-8-yl)-2-acetylaminofluorene, was detected only on the day following treatment at a concentration between 1.0 and 2.4 pmol/mg DNA. A second acetylated adduct, 3-(deoxyguanosin-N2-yl)-2-acetylaminofluorene, was found at both 1 and 14 days after treatment and, as a result, increased in concentration with repeated doses, from 0.2 pmol/mg DNA after one dose to 2.8 pmol/mg DNA after four treatments. The major adduct detected in male rat liver and the only adduct found in female rat liver and in kidney from either sex was N-(deoxyguanosin-8-yl)-2-aminofluorene. This adduct was slowly lost from the DNA and therefore increased in concentration with repetitive treatments as follows: male liver, 4.0 to 9.4 pmol/mg DNA; female liver, 11.4 to 30.6 pmol/mg DNA; male kidney, 1.1 to 1.8 pmol/mg DNA; and female kidney, 1.8 to 17.7 pmol/mg DNA. These data indicate that certain DNA adducts can accumulate in both target and non-target tissues and therefore suggest that persistence of DNA adducts per se is not sufficient for tumor induction. (Author abstract) (64 Refs)

7. EFFECTS OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF 2-ACETYLAMINOFLUORENE IN THE RAT.

Besbris HJ, Wortzman MS, Cohen AM
Sch. Pharmacy, Univ. Southern California, 1985 Zonal Ave., Los Angeles, CA, 90033
J Toxicol Environ Health; 9(1):63-76 1982

Effects of selenium on metabolism of 2-acetylaminofluorene (AAF) in male weanling CD rats were investigated. Animals were fed either a diet deficient in Se or the same diet supplemented wit h 0.5 ppm Se as sodium selenite. Hepatic microsomal metabolism of [9-14C]AAF (1 mCi/millimole) was measured in vitro. Microsomes from Se-deficient rats generated significantly less 3-OH-AAF than those from Se-supplemented animals. Only small amounts of N-OH-AAF were produced and no difference was noted between the two groups of animals. Moderately increased activity of glucuronyltransferase occurred in Se-deficient rats while hepatic soluble sulfotransferase activity was the same in both groups. Se-deficient rats excreted more of the given dose of AAF than did Se-supplemented rats; the increase was due to glucuronic acid- and sulfuric acid-conjugated metabolites and non-ether-extractable, water-soluble metabolites. Se-deficient rats excreted more N-OH-AAF, 7-OH-AAF, and 3-OH-AAF, while Se-supplemented rats excreted more 5-OH-AAF. Se-deficient rats excreted more of the administered dose of AAF as 7-OH-AAF than did Se-supplemented animals. A protective effect of dietary Se against AAF-induced hepatocarcinogenesis may be due in part to the inhibition of N-hydroxy-AAF production in vivo. (45 Refs)

8. METHOD OF ANALYSIS OF MONOTONE DOSE-RESPONSE PROBABILITIES AFTER LONG-TERM EXPOSURE TO A TOXICANT.

Scott BR
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890, Albuquerque, NM, 87185
Health Phys; 42(3):305-315 1982

A nonparametric hazard-function (HP) method for generating monotonically increasing incidence vs dose curves after long-term exposure to a toxic agent (eg radiation or chemical carcinogens) is described in detail in this paper. Here, incidence refers to the response-probability estimate that is adjusted for competing risks. The maximum likelihood principle was used to arrive at an appropriate point estimate of the cumulative hazard function (ie the negative natural logarithm of the proportion of nonresponders) and the response probability for an array of doses that depends on the data set to be analyzed. The resultant point estimates can be used to develop or select an appropriate model for risk vs dose assessment. As an example of the application of the HF method, data for liver neoplasms caused by long-term exposure of mice to 2-acetylaminofluorene and data for radiation pneumonitis and pulmonary fibrosis caused by long-term exposure of dogs to ionizing radiation are analyzed. (Author abstract) (15 Refs)

FLUORENAMINES: IN VITRO

9. PRIMARY CULTURE OF PRENEOPLASTIC HEPATOCYTES FROM RATS TREATED WITH 2-ACETYLAMINOFLUORENE AND CLOFIBRATE: RELATIONSHIP BETWEEN RESISTANCE TO DIMETHYLNITROSAMINE AND RESPONSIVENESS OF PEROXISOMES.

Sawada N, Furukawa K, Gotoh M, Mochizuki Y, Tsukada H
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan
Gan; 73(1):1-6 1982

Hepatocytes of 2-acetylaminofluorene-induced hyperplastic nodules of rats treated with clofibrate were transferred to primary culture after dispersion by a collagenase perfusion technique. After 48-hr treatment with dimethylnitrosamine (DMN), the resistance to the agent of the cells forming rod-shaped peroxisomes was examined. Catalase activity of the DMN-resistant cells was also determined. At concentrations of 10(-3) M and 10(-4) M DMN, the resistant cell population of hepatocytes with rod-shaped peroxisomes was larger than that of the cells without abnormal peroxisomes. On the other hand, the catalase activity of the attached cells that remained after DMN treatment decreased as the concentration of DMN was increased. The cells showing a stronger induction of the enzyme activity were found to be more sensitive to the cytotoxicity of DMN and they became detached from the culture dishes. (Author abstract) (21 Refs)

10. RELATIONSHIP BETWEEN THE GENETICALLY DETERMINED ACETYLATOR PHENOTYPE AND DNA DAMAGE INDUCED BY HYDRALAZINE AND 2-AMINOFLUORENE IN CULTURED RABBIT HEPATOCYTES.

McQueen CA, Maslansky CJ, Glowinski IB, Crescenzi SB, Weber WW, Williams GM
Div. Pathology and Toxicology, American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Proc Natl Acad Sci USA; 79(4,part1):1269-1272 1982

The relationship between acetylation rates of rabbit hepatocytes and their susceptibility to genotoxicity by DNA-damaging chemicals that undergo N-acetylation was studied in primary cultures of hepatocytes from New Zealand White rabbits that have a genetically determined difference in acetylation rates. Hepatocytes from rapid and slow acetylator rabbits maintained in culture the difference in acetylation rates that existed in vivo. DNA repair, an index of DNA damage, was produced by hydralazine in hepatocytes from slow acetylator rabbits but not in those from rapid acetylators. In contrast to these results, hepatocytes from rapid acetylators were more sensitive than those from slow acetylators to toxicity from the carcinogen 2-aminofluorene and displayed greater amounts of DNA repair. The amount of DNA repair measured with either chemical was dose dependent. These phenotype-dependent differences in the genotoxicity of two DNA-damaging chemicals provide evidence for the role of the acetylation polymorphism as a factor in determining susceptibility to toxicity, and perhaps carcinogenicity, of these chemicals. (Author abstract) (48 Refs)

11. CONFORMATION OF 2-[(DEOXYGUANOSIN-8-YLACETYL)AMINO]FLUORENE DIFFERS IN PROTEIN-FREE DEOXYRIBONUCLEIC ACID AND CHROMATIN.

Ross J, Metzger G, Werbin H
(c/o Werbin) Programs in Biology, Univ. Texas at Dallas, Richardson, TX, 75080
Biochemistry; 21(6):1369-1374 1982

There is substantial evidence that modification of protein-free DNA with 2-[(ace toxyacetyl)amino]fluorene results in the formation of 2-[(deoxyguanosin-8-ylacetyl)amino]fluorene adducts in which the fluorene ring inserts between the bases and the guanosine is shifted to the outside of the helix creating localized regions of denaturation. It was therefore of interest to determine the conformation of similarly induced adducts in chromatin and nucleosome core particles by circular dichroism, thermal denaturation, and single-strand-specific endonuclease susceptibility. Fluorenyl residues in modified chromatin and core particles gave rise to a less intense circular dichroism signal at 300 nm than those in purified DNA: approx-190 vs approx-280 deg cm2/nmol of fluorene residues, respectively. Levels of modification from 1.37 to 2.87 fluorenyl residues/100 nucleotides that produced a decrease of the melting temperature from 0.8 to 2.0 C in protein-free DNA had no effect upon the melting temperature of core particles. Adducts were not removed from modified core particles and chromatin by Neurospora crassa endonuclease as they were from modified DNA, even though this enzyme at the same concentration (12 units/A260 unit) recognized single-stranded regions introduced into the core particles by mild DNase I digestion. These data demonstrate minimal interaction of the fluorenyl residues with the DNA helix and provide no evidence for their induction of locally denatured regions. Hence, the existence of different conformations for modified bases in chromatin and protein-free DNA is proposed. The implications of this nondenaturing conformation with respect to the in vivo repair of these lesions are discussed, as well as the possibility that modified bases adopt a Z-DNA-like structure in modified chromatin as they do in modified poly(dG-dC)-poly(dG-dC). (Author abstract) (38 Refs)

12. DNA REPAIR IN HUMAN FIBROBLASTS TREATED WITH A COMBINATION OF CHEMICALS.

Ahmed FE, Setlow RB
Pharmacopathics Res. Lab., Laurel, MD, 20810
Biophys J; 35(1):17-22 1981

Photolysis of bromodeoxyuridine incorporated into parental DNA was used to study excision repair in normal human fibroblasts and xeroderma pigmentosum group C fibroblasts (XPC). The fibroblasts were treated with N-acetoxy-2-acetylaminofluorene (AAAF) and 4-nitroquinoline 1-oxide (4NQO). In normal and XPC cells, repair was additive after combined treatment with AAAF plus 4NQO. (13 Refs)

13. FORMATION AND IDENTIFICATION OF GLUTATHIONE CONJUGATES FROM 2-NITROSOFLUORENE AND N-HYDROXY-2-AMINOFLUORENE.

Mulder GJ, Unruh LE, Evans FE, Ketterer B, Kadlubar FF
(c/o Kadlubar) Natl. Center Toxicological Res., Dept. Health and Human Services, Jefferson, AR, 72079
Chem Biol Interact; 39(1):111-127 1982

The compounds 2-Nitrofluorene (NOF) and N-hydroxy-2-aminofluorene (N-HO-AF) are potent direct-acting mutagens, derived from metabolic activation of the carcinogen, N-acetyl-2-aminof luorene (AAF). To assess the ability of cellular glutathione (GSH) to detoxify these electrophilic derivatives, we examined the reaction of NOF and N-HO-AF with GSH in vitro. Two reaction products were isolated and identified as glutathionyl derivatives of 2-amino-fluorene (AF) containing an N-S linkage. Amino acid analysis, infrared and NMR (500 MHz) spectroscopy, fast atom bombardment mass spectrometry and analysis of reaction characteristics and hydrolysis products established their structures as N-(glutathion-S-yl)-2-aminofluorene S-oxide (GS-AF1) and N-(glutathion-S-yl)-2-aminofluorene (GS-AFII). Ascorbic acid, which reduces NOF to N-HO-AF, was used to modify reaction yields. These results indicated that GS-AF1 was derived from reaction with NOF and that GS-AFII could be formed from both NOF and N-HO-AF. A reaction scheme is proposed in which NOF reacts with GSH to form an intermediate addition product that can rearrange either to GS-AF1 or be reduced to GS-AFII. The latter could also be formed by direct reaction with N-HO-AF. (Author abstract) (50 Refs)

14. INFLUENCE OF LIVER S-9 PREPARATIONS FROM RATS AND RAINBOW TROUT ON THE ACTIVITY OF FOUR MUTAGENS.

De Flora S, Zanacchi P, Bennicelli C, Arillo A
Inst. Hygiene, Sch. Medicine, Univ. Genoa, 16132 Genoa, Italy
Toxicol Lett; 10(4):345-349 1982

The effects of rat and trout liver post-mitochondrial fractions on benzo(a)pyrene (BP), 2-aminofluorene (2-AF), aflatoxin B1 (AFB1), and sodium dichromate in the Ames reversion assay were compared. Rat preparations were significantly more efficient in activating AFB1 and 2-AF. Rat and trout preparations were equally effective in decreasing the direct mutagenicity of sodium dichromate. Rat microsomes were virtually ineffective and trout preparations were slightly active in producing mutagenic metabolites from BP. (14 Refs)

15. THE EFFECT OF LIVER POSTMITOCHONDRIAL FRACTION CONCENTRATION FROM AROCLOR 1254-TREATED RATS ON PROMUTAGEN ACTIVATION IN L5178Y CELLS.

Amacher DE, Turner GN
Dept. Safety Evaluation Dept., Pfizer Central Res., Groton, CN, 06340
Mutat Res; 97(2):131-137 1982

Mouse L5178Y/TK+/- cells (strain 3.7.2C) were exposed to N-acetyl-2-aminofluorene (AAF: 50 or 67 ug/ml), 2-aminoanthracene (AA: 0.96 ug/ml), benzanthracene (BA: 7.35 ug/ml), benzo(a)pyrene (BP: 2.5 ug/ml), dimethylnitrosamine (DMN: 74.1 ug/ml), or 3-methylcholanthrene (MCA: 5.4 ug/ml), in the presence of varying concentrations (2.5-10%, vol/vol) of liver S9 postmitochondrial fraction from Aroclor-treated male CD rats. With AAF, AA, BA, BP, and MCA, the occurrence of trifluorothymidine-resistant mutants (TFTr) declined in proportion to increases in the S9 concentration during the 3-hr incubation period. With DMN, the occurrence of TFTr mutants increased moderately in proportion to increases in the S9 concentration during the 3-hr incubation period. The results suggest that two different metabolic events may be involved: activation via non-induced factors (perhaps enzymes) whose activities are totally dependent on the vol of S9 (DMN), and deactivation via induced detoxification pathways in a sequence favored by increasing the S9 concentration (the other promutagens tested). The use of a 'standard' concentration (10%) of rat liver S9 did not seem to provide optimal metabolic activation for any of the promutagens except DMN. With the other promutagens, the greatest degree of activation was observed at the lowest S9 concentration studied. (11 Refs)

16. DEFICIENT REPAIR OF CHEMICAL ADDUCTS IN ALPHA DNA OF MONKEY CELLS.

Zolan ME, Cortopassi GA, Smith CA, Hanawalt PC
Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305-2493
Cell; 28(3):613-619 1982

We have examined excision repair of DNA damage in the highly repeated alpha DNA sequence of cultured African green monkey cells. Irradiation of cells with 254 nm ultraviolet light resulted in the same frequency of pyrimidine dimers in alpha DNA and the bulk of the DNA. The rate and extent of pyrimidine dimer removal, as judged by measurement of repair synthesis, was also similar for alpha DNA and bulk DNA. In cells treated with furocoumarins and long-wave-length ultraviolet light, however, repair synthesis in alpha DNA was only 30% of that in bulk DNa, although it followed the same time course. We found that this reduced repair was not caused by different initial amounts of furocoumarin damage or by different sizes of repair patches, as we found these to be similar in the two DNA species. Direct quantification demonstrated that fewer furocoumarin adducts were removed from alpha DNA than from bulk DNA. In cells treated with another chemical DNA-damaging agent, N-acetoxy-2-acetylaminofluorene, repair synthesis in alpha DNA was 60% of that in bulk DNA. These results show that the repair of different kinds of DNA damage can be affected to different extents by some property of this tandemly repeated heterochromatic DNA. To our knowledge, this is the first demonstration in primate cells of differential repair of cellular DNA sequences. (Author abstract) (33 Refs)

17. A MODEL FOR THE EFFECT OF EXCISION REPAIR ON THE SURVIVAL OF HUMAN CELLS EXPOSED TO CHEMICAL CARCINOGENS.

Miller JH, Heflich RH
Pacific Northwest Lab., Richland, WA, 99352
Chem Biol Interact; 39(1):45-55 1982

A model is presented which correlates the survival of normal human fibroblasts (NF) after exposure to N-acetoxy-2-acetylaminofluorene (N-AcO-AAF) with the rate of excision of carcinogen residues bound to DNA. Measurements of the rate of excision of carcinogen residues suggest that this is a first-order process with 37% of the adducts remaining after about 70 hr. From this information and the dose-response relationship for survival of NF and repair deficient cells we can determine the mean number of adducts required to produce a potentially lethal lesion and the effective time available for repair. When these adjustable parameters have been determined, we can use the model to predict the rate of excision in partially repair-deficient cells and the effect of extending the repair period by arresting cell growth after treatment. Survival studies in which cells were held at confluence for varying amounts of time between treatment and replating at low density show good agreement with the predictions of the model. (Author abstract) (14 Refs)

18. A REDUCED CAPACITY FOR UNSCHEDULED DNA SYNTHESIS IN LYMPHOCYTES FROM INDIVIDUALS EXPOSED TO PROPYLENE OXIDE AND ETHYLENE OXIDE.

Pero RW, Bryngelsson T, Widegren B, Hogstedt B, Welinder H
Wallenberg Lab., Biochemical and Genetic Ecotoxicology, Univ. Lund, Box 7031, S-220 07 Lund 7, Sweden
Mutat Res; 104(1-3):193-200 1982

Inhibition of unscheduled DNA synthesis (UDS) was studied in 23 workers (25-59 yr old, mean age 41 yr) exposed to propylene oxide (PO) as process workers for 1-20 yr (mean 10 yr) and in 5 male workers (25-44 yr old, mean age 32 yr) exposed to ethylene oxide (EO) as sterilizing, packing, or truck-driving personnel for 0.3-5 yr (mean 2.9 yr). Eighteen of 23 PO-exposed workers were smokers. Controls were 12 male workers (21-46 yr old, mean age 30 yr) not exposed occupationally to any mutagenic chemical compound. Five of the controls were smokers. UDS induced by N-acetoxy-2-acetylaminofluorene (NA-AAF) and NA-AAF binding to DNA were the methods used. Use of [3H]NA-AAF enabled the direct assessment of initial NA-AAF damage to DNA, which in turn served as the substrate for induction of UDS, and thereby repair of NA-AAF lesions in the DNA. Lymphocyte samples from both the controls and the PO-exposed workers varied considerably in values for NA-AAF-induced UDS. UDS variation was dependent on the level of NA-AAF bound to DNA after a 30-min incubation of lymphocytes in the presence of 10 uM [3H]NA-AAF. The correlation coefficients between NA-AAF-induced UDS and NA-AAF binding to DNA were highly significant for both the controls and PO-exposed workers. PO- plus EO-exposed workers exhibited significant reductions in NA-AAF-induced UDS when compared to the controls. The level of [3H]NA-AAF covalent binding to DNA was not significantly reduced by PO- and EO-exposure. Results indicate that exposure to relatively low doses of PO and EO can cause individuals to be at increased risk due to a reduced capacity to repair DNA lesions. (12 Refs)

19. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein E
Gulf South Res. Inst., New Orleans, LA
Sci Tech Aerosp Rep; 19(24):3372 1981

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater or in yields of 40% or more from Lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. (Author abstract) (no Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

20. BENZIDINE LEVEL IN THE URINE OF RATS SUBJECTED TO ADMINISTRATION OF BENZIDINE DYES.

Zhdan VM, Pylev LN
All-Union Cancer Res. Center, Moscow, USSR
Gig Tr Prof Zabol; (1):32-35 1982

To evaluate the mechanism of carcinogenic activity of benzidine (BD), random-bred female rats were subjected to a single, ip or intragastric administration of direct dyes. The urine of exposed animals contained BD. The highest levels of BD were observed after administration of direct blue K and direct diazoblack C. (7 Refs) (In RUS)

21. CARCINOGENICITIES OF 3-METHOXY-4-AMINOAZOBENZENE, N-HYDROXY-3-METHOXY-4-AMINOAZOBENZENE AND RELATED AZO DYES IN THE MOUSE.

Watanabe HK, Hashimoto Y, Abe I, Sato H
Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 73(1):136-140 1982

The carcinogenicities of 2-methoxy-4-aminoazobenzene and 3-methoxy-4-aminoazobenzene (2-MeO-AAB and 3-MeO-AAB) and their N-hydroxy derivatives (N-OH-2-MeO-AAB and N-OH-3-MeO-AAB) were tested in (C3H x C57BL/6) F1 mice. Topical sc injections, twice weekly for 8 wk, of 4 or 8 umol of N-OH-3-MeO-AAB dissolved in 0.1 ml of olive oil containing 10% dimethyl sulfoxide induced fibrosarcomas at the site of application. Similar treatment with 3-MeO-AAB or 2-MeO-AAB as well as N-OH-2-MeO-AAB failed to induce sarcomas. Oral administration of 0.09% 3-MeO-AAB in the diet for 13 mo induced hepatic tumors in female mice but not in males. 2-MeO-AAB did not induce tumors in male or female mice. The relationship between carcinogenicity, mutagenicity, the ability to induce unscheduled DNA synthesis, and the metabolism of these azo dyes is discussed. (Author abstract) (18 Refs)

22. MATRICAL INCLUSIONS OF PEROXISOMES INDUCED BY CLOFIBRATE IN PRENEOPLASTIC HEPATOCYTES OF RATS FED 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE.

Gotoh M, Mochizuki Y, Sawada N, Tsukada H
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan
Gan; 73(1):7-13 1982

The response of peroxisomes to clofibrate in preneoplastic hepatocytes of rats fed 3'-methyl-4-dimethylaminoazobenzene was examined histochemically (using the 3,3'-diaminobenzidine reaction) and electron microscopically. Morphometrical examinations revealed that the numb er of peroxisomes correlated well with the intensity of the histochemical reaction. Preneoplastic hepatocytes which responded to clofibrate with a marked proliferation of peroxisomes showed no matrical inclusions or merely matrical plates in very low incidence in the proliferated peroxisomes. The cells that exhibited a moderate proliferation of peroxisomes showed formation of peroxisomal matrical inclusions in high incidence. The inclusions were matrical plates and tubules showing the same fine structures as those found in 2-acetylaminofluorene carcinogenesis. These peroxisomal inclusions were absent in the cells which responded to clofibrate with no or only a slight increase in the number of peroxisomes. It is suggested that these varieties of peroxisomal changes might reflect the progress of preneoplastic phases of the cells. (Author abstract) (11 Refs)

23. THE CHARACTERIZATION OF TRYPAN BLUE-INDUCED TUMORS IN WISTAR RATS.

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Am J Pathol; 106(3):326-331 1982

Trypan blue is an azo dye widely used for testing cell viability. The dye has been identified as a mutagen and a carcinogen. In some strains of rats, particularly Wistar rats, chronic exposure induces a reticuloendothelial neoplasm, predominantly in the liver. These tumors were studied with the use of immunologic cell membrane markers, electron microscopy, and histochemistry to characterize tumor cell type. The authors have studied this tumor in two inbred lines of Wistar rats to compare the efficacy of two previously described dye regimens on tumor incidence and to ascertain whether a short, intense exposure was as effective as chronic protracted exposure. No significant difference in tumor incidence was observed between the two regimens. These studies suggest that the tumor is composed of a macrophage-like cell that retains some characteristics of normal macrophages and that it is a reproducible model for carcinogen-induced lymphoreticular disease that may be of value in the study of some human lymphomas. (Author abstract) (22 Refs)

24. HEPATOCYTES WITH EXTRAPEROXISOMAL CATALASE IN RATS FED 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE.

Gotoh M, Mochizuki Y, Furukawa K, Sawada N, Tsukada H
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Gan; 73(1):14-20 1982

Histochemical and cytochemical studies were done to further characterize the preneoplastic hepatocytes with extraperoxisomal catalase (EPC-cells) that were found in the livers of rats fed 3'-methyl-4-dimethylaminoazobenzene. Catalase activity was demonstrated cytochemically to be localized in nuclear matrices, hyaloplasm, and peroxisomal matrices of EPC-cells. It is suggested that an impairment of peroxisome formation is involved in the altered intracellular distribution of catalase. Administration of clofibrate increased the catalase activity in EPC-cells. To examine the preneoplastic nature of EPC-cells, activities of glucose-6-phosphatase (G6Pase) and gamma-glutamyl transpeptidase (GGT) were examined, since changes in the activities of these enzymes have been used as markers of putative preneoplastic cells. In the present study, neither weak G6Pase activity nor positive GGT activity was considered to be a consistent feature of EPC-cells. However, available evidence suggests that EPC-cells are one of the carcinogen-induced cell populations with altered phenotypes. (Author abstract) (16 Refs)

25. FORMATION OF N-(GLUTATHION-S-METHYLENE)-4-AMINOAZOBENZENE FOLLOWING METABOLIC OXIDATION OF THE N-METHYL GROUP OF THE CARCINOGEN, N-METHYL-4-AMINOAZOBENZENE.

Ketterer B, Srai SK, Waynforth B, Tullis DL, Evans FE, Kadlubar FF
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Chem Biol Interact; 38(3):287-302 1982

A major biliary metabolite of the hepatocarcinogen, N,N-dimethyl-4-aminoazobenzene (DAB), in the rat was identified as N-(glutathion-S-methylene)-4-aminoazobenzene (GS-CH2-AB). This conjugate was prepared synthetically by a Mannich condensation of 4-aminoazobenzene (AB), formaldehyde (CH2O) and glutathione (GSH) and has been characterized by chemical analysis and by ultraviolet, visible and 13C-NMR spectroscopy. The same conjugate was also formed in vitro by incubating N-methyl-4-aminoazobenzene (MAB), NADPH, NADH and GSH with rat hepatic microsomes. Evidence is presented that GSH reacted with an intermediate resulting from a cytochrome P-450-dependent oxidation of the N-methyl substituent. This reactive intermediate is presumed to be either an N-methylol or a methimine derivative of AB. The significance of this detoxification mechanism is discussed. The presence of an additional major aminoazo-dye GSH conjugate is also noted. (Author abstract) (31 Refs)

26. THE HISTOCHEMICAL DEMONSTRATION OF GAMMA-GLUTAMYL TRANSPEPTIDASE ACTIVITY IN DIFFERENT POPULATIONS OF RAT LIVER CELLS DURING AZO DYE CARCINOGENESIS.

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J Histochem Cytochem; 30(4):312-316 1982

To better assess the reliability of gamma-glutamyl transpeptidase (gamma-GTase) as a marker of preneoplastic liver lesions and hepatomas, the gamma-GTase activity of different cell populations was examined in liver sections from rats fed 4-dimethylaminoazobenzene. The results indicated that the biliary ductular cells in trabeculae of cirrhotic livers may exhibit appreciable gamma-GTase activity in addition to that shown by islands of regenerating parenchyma. At later stages of azo dye carcinogenesis, the epithelial cells of bile duct cysts and cholangiomas, as well as those of hepatomas, gave positive reactions for gamma-GTase. Thus biochemical data on liver gamma-GTase in different models of hepatocarcinogenesis cannot be translated directly in terms of alterations in a particular cell type unless such interpretation is justified by parallel histochemical investigations. (Author abstract) (63 Refs)

27. N-HYDROXYLATION ENZYMES OF CARCINOGENIC AMINOAZO DYES: POSSIBLE INVOLVEMENT OF CYTOCHROME P-448.

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Gan; 73(1):55-62 1982

N-Hydroxylation reactions of 3'-methyl-N,N-dimethyl-4-aminoazobenzene (3'-Me-DAB) and 3'-methyl-N-methyl-4-aminoazobenzene (3'-Me-MAB) were studied by measuring the nitroxide radical generated from N-hydroxylated products of these aminoazo compounds. N-Hydroxylation activity was remarkably high in the microsomes from 3-methylcholanthrene (3-MC)-treated rats, whereas phenobarbital (PB) treatment had a slightly enhancing effect on the N-hydroxylation of 3'-Me-DAB and a rather inhibitory effect on that of 3'-Me-MAB. Either NADPH or NADH was effective for the N-hydroxylation of 3'-Me-MAB, though the former was slightly more effective. For the reaction of 3'-Me-DAB the effect of NADPH and NADH was additive, but this was not the case for 3'-Me-MAB. Carbon monoxide, metyrapone and 2-dimethylaminoethyl-2,2-diethylvalerate hydrochloride (SKF-525A), inhibitors of cytochrome P-450, had no inhibitory effect on the N-hydroxylation of 3'-Me-DAB and 3'-Me-MAB. On the other hand, alpha-naphthoflavone, an inhibitor of cytochrome P-448, considerably inhibited the N-hydroxylation of these aminoazo dyes. In the case of partially purified mixed function amine oxidase (MFAO), 1-(1-naphthyl)-2-thiourea, an inhibitor of MFAO, completely inhibited the N-hydroxylation of 3'-Me-MAB as well as the N-oxidation of dimethylaniline. On the other hand, in a microsomal system the inhibition of the N-hydroxylation was at most 40% at the concentration giving complete inhibition of the N-oxidation of dimethylaniline. From these results, it is concluded that, in addition to MFAO, cytochrome P-448 is involved in the N-hydroxylation of MAB. (Author abstract) (26 Refs)

28. A FREE RADICAL MECHANISM FOR ARYLAMINE INDUCED CARCINOGENESIS INVOLVING PEROXIDES.

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Biochem Pharmacol; 31(4):607-608 1982

A 1 e oxidation of N-methyl-4-aminoazobenzene (MAB) catalyzes more binding than the 2 e monooxygenase mechanism in the presence of liver sulfotransferase. Covalent binding of (14C)MAB metabolites to exogenous DNA or microsomal protein demonstrated that hydroperoxide was almost 400x more effective than NADPH in catalyzing the binding. NADPH/reductase may reduce the radical formed by the 1 e oxidation pathway of cytochrome P450. The hydroperoxide catalyzed binding was not affected by addition of cytosol, while the NADPH system was markedly enhanced. Addition of ATP and sulfate further enhanced the cytosol effect, suggesting that the cytosol effect was probably due to sulfotransferase acting on the NOH MAB formed by the 2 e oxidation pathway carried out by microsomal amine oxidase/4. No NOH MAB was formed with hydroperoxide. Cytochrome P450 catalyzed both N demethylation and ring hydroxylation of MAB and the N hydroxylation was catalyzed by microsomal amine oxidase. In dogs and mice, the 1 e pathway of the monooxygenase activity of bladder and lung tissue may be responsible for carcinogenesis in these organs following administration of p-dimethylaminoazobenzene. In mouse liver carcinogenesis, both the 1 e and 2 e pathways should be considered. (9 Refs)

29. COMPARISONS BETWEEN CARCINOGENIC POTENCY AND MUTAGENIC POTENCY TO SALMONELLA IN A SERIES OF DERIVATIVES OF 4-DIMETHYLAMINOAZOBENZENE (DAB).

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Mutat Res; 93(1):67-81 1982

The carcinogenic and mutagenic potencies of 4-dimethylaminoazobenzene (DAB) and several derivatives of DAB were compared. Test compounds were 5-phenylazoindazole (5I), 6-phenylazoindazole (6I), 7-phenylazoindazole (7I), 5-phenylazobenzothiazole (5BT), 6-phenylazobenzothiazole (6BT), and 7-phenylazobenozothiazole (7BT). Reference compounds were DAB, the noncarcinogen 4'-dimethylamino-4-dimethylaminoazobenzene (Compound II), and the potent carcinogen 2'3'-dimethyl-4-dimethylaminoazobenzene (Compound III). S9 mix was prepared from livers of male Sprague-Dawley rats treated with Aroclor 1254. Mutagenicity was measure in Salmonella typhimurium strain TA98 in plate-incorporation (PI), liquid pre-incubation (LPI), and fluctuation tests. DAB, 5I, and 6BT were tested by ip injection into Alderley Park rats; liver tissue was examined 6 hr after injection. Results of the PI test were negative for DAB and positive for all other compounds. Results of the LPI test were positive for all compounds. The results of the fluctuation test were positive for DAB, 5I, 6I, 7I, 5BT, 6BT, and 7BT and negative for Compounds II and III. DAB and 6BT produced pathological changes in rat liver and affected the recovery profile of methylated bases derived from hepatic DNA of pretreated rats; 5I did not. The value of short-term in vivo assays, including the potential to identify potent mammalian carcinogens among structurally related compounds, is discussed. (45 Refs)

30. ANALYSIS OF A METHOD FOR TESTING AZO DYES FOR MUTAGENIC ACTIVITY IN SALMONELLA TYPHIMURIUM IN THE PRESENCE OF FLAVIN MONONUCLEOTIDE AND HAMSTER LIVER S9.

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Mutat Res; 97(2):103-116 1982

A protocol was developed for assessing the mutagenicity of azo dyes derived from mutagenic or potentially mutagenic aromatic amines in Salmonella typhimurium TA98. In the protocol, uninduced hamster liver S9 (150 ul) is used instead of Aroclor 1254-induced rat liver S9 (max, 50 ul) in the standard assay; flavin mononucleotide is used instead of riboflavin to reduce the azo compounds to free amines; the cofactor mix is modified to include exogenous glucose 6-phosphate dehydrogenase, NADPH, and 4x the standard amount of glucose-6-phosphate; and 30 min of preincubation is performed before the top agar is added. All of the modifications were necessary for optimal mutagenic activity of the azo dyes tested: Congo red (CR), benzopurpurine 4B (BP4B), trypan blue (TB), and Direct Blue 1 (DB1). The assay was also performed using known or probable reduction products of the dyes having known mutagenic and carcinogenic activity: benzidine (BZD; a reduction product of CR), o-tolidine (o-TD: a reduction product of BP4B and TB), and o-dianisidine (o-DAD: a suspected reduction product of DB1). The mutagenicities of CR, TB, and DB1 were greater when hamster liver S9 was substituted for rat liver S9. BZD was more mutagenic with hamster liver S9 than with rat liver S9, but o-TD and o-DAD were not. Rat liver S9 inhibited the ability of hamster liver S9 to activate BZD to a mutagen. The presence in rat liver S9 of an inhibitor of BZD metabolic activation may account for the failure of BZD and a BZD dye (CR) to be strongly mutagenic in the presence of rat liver S9. (27 Refs)

31. EMBRYOTOXICITY OF 3,3',4,4'-TETRACHLOROAZOBENZENE AND 3,3',4,4'-TETRACHLOROAZOXYBENZENE IN THE CHICK EMBRYO.

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Arch Environ Contam Toxicol; 11(2):195-202 1982

The chick embryo assay was run on F1(NH x SCWL) chicken eggs given a single air cell injection of 0.0001-100 ug of 3,3',4,4'-tetrachloroazobenzene (TCAB) or 0.0005-100 ug of 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) on days 4 (all doses) or 11-13 (only 0.05 ug) of incubation. LD50 for TCAB was 44 ng, and for TCAOB, 12 ng. The incidence of severe, non-dose related sc edema from 0.01-1.0 ug of TCAB was 2.5-5.1%, and from 0.005-0.05 of TCAOB was 2.1-22.5%. Other malformations included altered feather pattern and lack of down, hemorrhage, external viscera, reduced body size, failure to withdraw the yolk sac, beak malformation, dilation of blood vessels, and monomicropthalmia. (38 Refs)

32. TRANSCRIPTS OF CELLULAR ANALOG OF VIRUS SARCOMA SRC GENE IN MOUSE LIVER.

Mett VL, Chumakov IM, Kiselev LL
Inst. Molecular Biology, Moscow, USSR
Dokl Akad Nauk SSSR; 261(6):1471-1472 1981

Analysis of the expression of protosarc gene in the liver of mice uninfected with Moloney sarcoma virus (MSV) showed synthesis of poly(A)-RNA homologous to RNA of MSV. Poly(A)-RNA showing hybridization with src gene of MSV were also detected in the liver of mice treated with the hepatocarcinogen o-aminoazotoluene. These findings can indicate transcription of the endogenous sarcoma provirus during chemical carcinogenesis. (7 Refs) (In RUS)

33. HIGH UPTAKE OF 14C-LABELED D-AMINO ACIDS BY VARIOUS TUMORS.

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Gan; 73(1):147-152 1982

As an extension of the previous finding that radioactivity of 14C-labeled D-amino acids after injection is localized preferentially in the tumor and the pancreas of tumor-bearing animals as compared with the corresponding L-amino acids tested, the results of similar uptake experiments using other tumors are reported here. The present studies show high radioactivity uptake by human colon cancer, human thyroid cancer, and human leiomyosarcoma transplanted into nude mice, and by solid leukemia L1210 and solid sarcoma 180, but not by Morris hepatoma 7316A or 3'-methyl-4-(dimethylamino)azobenzene-induced rat hepatoma. The results suggest the potential utility of 11C-labeled D-amino acids for the detection of some cancers. (Author abstract) (14 Refs)

HETEROCYCLIC AMINES

34. MUTAGENIC AND ALKYLATING ACTIVITIES OF 3-METHYL-1-PHENYLTRIAZENES AND THEIR POSSIBLE ROLE AS CARCINOGENIC METABOLITES OF THE PARENT DIMETHYL COMPOUNDS.

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Cancer Res; 42(4):1446-1453 1982

The compound 3-methyl-1-phenyltriazene and a series of ring-substituted derivatives (4-methylphenyl, 4-chlorophenyl, and 2,4,6-trichlorophenyl), structurally related benzenediazonium fluoborates and phenyl azides, as well as the recently isolated [1-methyl-3-(2,4,6-trichlorophenyl)-2-triazeno]methyl beta-D-glucopyranoside uronic acid, were studied for their mutagenic activity in Salmonella typhimurium strains. Of these compounds, the 3-methyl-1-phenyltriazene derivatives and 2,4,6-trichlorobenzenediazonium fluoborate were found to be direct-acting mutagens; the glucuronide was active in strain TA 1530 only after deconjugation with beta-glucuronidase. The half-lives of the monomethylphenyltriazenes in vitro were determined and compared with their methylating activity towards 4-(4-nitrobenzyl)pyridine and their mutagenicity. The results are discussed in relation to the possible mechanism of action of the N,N-dimethylphenyltriazenes and their monomethyl derivatives as mutagens and organ-specific carcinogens. (Author abstract) (43 Refs)

35. CYTOGENETIC ACTIVITIES OF 3 SULPHONAMIDES.

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Mutat Res; 104(1-3):95-100 1982

Cytogenetic effects of three sulfonamides were tested in Allium cepa (cv Giza). Bulbs with growing root tips were exposed to sulfadiazine (2-p-aminobenzene sulfonamide pyrimidine), sulfadimidine (2-p-aminobenzene sulfonamide 5-p-aminomethyl pyrimidine), or sulfaphenazole (5-p-aminobenzene sulfonamide-1-phenyl pyrazole) at concentrations of 0.02, 0.2, 1.0, or 2.0 mg/ml for 4, 24, or 48 hr. Cytological effects were studied by means of the Feulgen squash technique. Compared with controls, mitotic indices (MI) were increased by all three test compounds after 4-hr exposures and reduced after 24-and 48-hr exposures. Reduction in MI were concentration-dependent. Increasing exposure time from 24 to 48 hr produced only slight additional reduction in MI. MI were reduced to less than 50% of control values by concentrations of 1 or 2 mg/ml. All three test compounds produced high frequencies of mitotic and chromosomal abnormalities (C-metaphases, multipolar mitoses, polyploidy, chromosome lagging, stickiness, bridges, and breakage) after 4-hr exposures. The frequency of abnormalities was decreased after 24-hr exposures and increased relative to 24-hr exposures by 48-hr exposures. Wide variations were observed among roots undergoing the same treatment. Mitotic abnormalities were more common after 4-hr exposures, while chromosomal abnormalities were more common after 24-or 48-hr exposures. Results suggest possible mutagenic effects in humans. (18 Refs)

36. CORRELATION OF ALKYLATING AND MUTAGENIC ACTIVITIES OF ALLYL AND ALLYLIC COMPOUNDS: STANDARD ALKYLATION TEST VS. KINETIC INVESTIGATION.

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Chem Biol Interact; 38(3):303-315 1982

Thirty-nine allylic and non-allylic compounds have been tested in the standard 4-(p-nitrobenzyl)pyridine (NBP) alkylating procedure and the Salmonella typhimurium mutagenicity assay. Fourteen of these were found directly mutagenic (without addition of S-9 mix activating enzyme system). With 12 of these compounds, a good correlation of alkylating and mutagenic potencies was established; the remaining 2 do not meet the chemical conditions of the NBP procedure on account of HCL elimination with these 2 compounds. The other 25 substances were inactive in both systems. The quantitative correlation proved to be almost linear in the lower activity ranges (E approx 2; revertants/umol approx 600). The reasons for some deviations from the linear relationship have been analyzed and discussed on the basis of structural features. In addition to the standard alkylation test, a modified NBP-test was performed in order to obtain kinetic data and activation energy values. The results with six representative allylic compounds show that the overall correlation is not substantially improved above that of the standard procedure; nonetheless, additional information on reaction characteristics is obtained with some substances. (Author abstract) (26 Refs)

37. COMPARATIVE MUTABILITY OF THE AMES TESTER STRAINS OF SALMONELLA TYPHIMURIUM BY ULTRAVIOLET RADIATION AND BY 4-NITROQUINOLINE 1-OXIDE.

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Mutat Res; 93(1):35-44 1982

Relative mutability of five tester strains of Salmonella typhimurium and the kinetics of reverse mutation were studied after exposure to UV or 4-nitroquinoline 1-oxide (4NQO). Following UV irradiation, strain TA1538 was non-mutable; the other strains were mutable in the order TA100 greater than TA1535 greater than TA98 = TA1537. Following exposure to 4NQO the strains were mutable in the order TA100 greater than TA1538 greater than TA98 greater than TA1535 greater than TA1537. Mutability differences in relation to 'hot spot' base sequences and the nature of DNA damage are discussed. (18 Refs)

38. ABNORMAL SENSITIVITY OF SKIN FIBROBLASTS FROM FAMILIAL POLYPOSIS PATIENTS TO DNA ALKYLATING AGENTS.

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Cancer Res; 42(4):1249-1254 1982

Fibroblast cell strains derived from patients afflicted with genetic diseases predisposing to the development of intestinal polyposis and cancer were tested for their sensitivity to the effects of the DNA alkylating agents methyl methanesulfonate (MMS), ethyl methanesulfonate, N-methyl-N'-nitro-N-nitrosoguanidine, and 4-nitroquinoline 1-oxide. The genetic syndromes studied were: adenomatosis of the colon and rectum only, an autosomal dominant trait; Turcot's syndrome, a rare autosomal recessive polyposis syndrome also characterized by central nervous system tumors; and Gardner's syndrome, an autosomal dominant syndrome which, in addition to intestinal polyposis, is also clinically characterized by osteomas and soft tissue tumors. Survival of the various polyposis fibroblast strains was compared to the av survival of three normal human fibroblast strains by t test analysis of the respective values for the inverse of the slope of the survival curve and the concentration resulting in 10% survival. Fibroblasts from the patient with adenomatosis of the colon and rectum (strain GM2355) were moderately but significantly sensitive to 4-nitroquinoline 1-oxide. In addition, strain GM2355 was significantly more sensitive to ethyl methanesulfonate. Fibroblasts from the patient with Turcot's syndrome were hypersensitive to MMS. Fibroblasts from the Gardner's syndrome proband were moderately sensitive to MMS, ethyl methanesulfonate, and N-methyl-N'-nitro-N-nitrosoguanidine. Fibroblasts from the clinically affected Gardner's syndrome daughter of the proband were significantly more sensitive to MMS treatment. This differential sensitivity to the several DNA alkylating agents suggests that different mechanisms of hypersensitivity to these chemicals may be associated with fibroblasts from the various forms of familial polyposis. (48 Refs)

39. THE MUTAGENIC POTENCY OF 1,8-DINITROPYRENE IN CULTURED MOUSE LYMPHOMA CELLS.

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Mutat Res; 93(1):213-220 1982

The mutagenic potency of 1,8-dinitropyrene (1,8-DNP) was compared with that of 4-nitroquinoline-1-oxide (4NQO) in cultured mouse lymphoma cells. L5178Y cells were grown in suspension culture and cloned in semisolid medium. 1,8-DNP and 4NQO were dissolved in dimethylsulfoxide (DMSO). DMSO alone had no effect on growth, cloning efficiency, or mutation frequency. Mutagenicity of test compounds was measured as the frequency of induction of resistance to 6-thioguanine (TG), methotrexate (MTX), ouabain (OUA), or 1-beta-D-arabinofuranosyl cytosine (ARA-C). Max mutation frequencies were obtained with 48-96-hr exposures for OUA, ARA-C, and MTX and with 144-192-hr exposures for TG. 1,8-DNP was not toxic at concentrations up to the max 2.5 ug/ml. Both 1,8-DNP and 4NQO produced dose-dependent increases in mutation frequencies in all mutation systems. Mutations evidently occurred by base-pair substitutions. Since previous studies had shown that 1,8-DNP produces frame-shift mutations in Salmonella and Escherichia coli, results suggest that 1,8-DNP produces mutations by different mechanisms in bacteria and mammalian cells. Problems of comparing mutagenicity of test chemicals when concentrations, treatment times, and toxicity are significantly different are discussed. (20 Refs)

40. IN VITRO ALKYLATION TESTS: COMPARISON OF THE ALKYLATION RATE AND MUTAGENICITY.

Hemminke K, Falk K, Vainio H
Inst. Occupational Health Care, Helsinki, Finland
Gig Tr Prof Zabol; (1):43-44 1982

Alkylating activity of a series of epoxy-containing compounds was studied in 4-(p-nitrobenzyl)-pyridine and deoxyguanosine tests. The alkylation rate showed a correlation with the mutagenic activity. These findings indicate that simple in vitro alkylation tests can be used for the preliminary estimation of the mutagenicity. (7 Refs) (In RUS)

REVIEWS AND OTHER RELATED STUDIES

41. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.

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Mutat Res; 98(2):101-248 1982

Genetic hazards associated with the production and use of synthetic and natural dyes used as food additives are reviewed. Genotoxicity of structurally-related azo, triphenylmethane and xanthene dyestuffs used in drugs and cosmetics was considered. Particular attention was given aminoazobenzene and several of its derivatives with respect to carcinogenicity and mutagenicity. Activities of these dyes in short-term tests for genotoxicity are stressed; animal carcinogenicity and nonspecific toxicity is not emphasized. Dye metabolism and activities of dye metabolites are reviewed. Structural features of these dyes and their metabolites were assessed and an attempt was made to evaluate data with respect to correlations with tumor-inducing ability and to levels of environmental exposure. More than half of the dyes discussed have shown activity in at least one short-term test. Certain food colors may be active in vitro at levels comparable to those ingested daily. Natural colors, except for curcumin and riboflavin, were inactive. More data are required for all of the various dye groups, particularly for synthetic and natural non-azo compounds. Discussion of structure-activity must be tentative because of the lack of data and problems due to active sample contaminants. The presence of various substituents may be potentiating. No currently permitted food color which is inactive in short-term tests is considered a carcinogen, although some active colors require further animal testing. A human cancer hazard may exist where significant amounts of finished benzidine dye samples are handled. Such risks from exposures to other colors and the possibility of human germ-line mutation induction by dyes cannot be assessed in a meaningful manner. (365 Refs)

42. QUANTITATIVE CORRELATIONS AMONGST ALKALINE DNA FRAGMENTATION, DNA COVALENT BINDING, MUTAGENICITY IN THE AMES TEST AND CARCINOGENICITY, FOR 21 COMPOUNDS.

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Mutat Res; 93(1):1-24 1982

Correlations between the carcinogenicity of 21 compounds and the alkaline DNA fragmentation, formation of DNA adducts, and Ames-test mutagenicity produced by the compounds were studied. Test compounds included 6 methylating agents, 3 ethylating agents, 5 aromatic amines, 2 polycyclic aromatic hydrocarbons, and 5 heterogeneous compounds thought to generate DNA adducts with greater steric hindrance than those produced by methylating or ethylating agents. Compounds were administered to adult mice and rats by oral and parenteral routes. The highest doses exceeded lethal levels. Parameters measured included the oncogenic potency index (OPI), covalent binding index (CBI), DNA fragmentation index (DFI), mutagenic potency index (MPI), and lethal dose index (LDI). All parameters were found to be correlated with carcinogenic potency; the correlation between CBI in vivo and carcinogenicity was 3x as great as the correlation between the MPI and carcinogenicity. CBI in vivo correlated strongly with DFI in vivo. Assay of the DFI for eight compounds indicated negative results for benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, 2-acetylaminofluorene, and urethane; positive results were obtained for methyl methanesulfonate, aniline, 2-naphthylamine, and benzidine. Results indicate that carcinogenic potential should be predictable from the results of a battery of appropriate tests. (28 Refs)

43. BIOLOGICAL OXIDATION OF NITROGEN IN ORGANIC COMPOUNDS AND DISPOSITION OF N-OXIDIZED PRODUCTS.

Hlavica P
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CRC Crit Rev Biochem; 12(1):39-101 1982

The most important findings concerning biotransformation of nitrogen-containing molecules to N-oxidized products, including mutagens and carcinogens, are reviewed. Chemical aspects, including classification and chromatographic methods, and occurrence of N-oxidation products in microorganisms, plants, and animals are discussed. N-oxidation of amine compounds is reviewed, with a list of compounds shown to be excreted in the urine as N-oxidation products. Enzymology of N-oxidation in the endoplasmic reticulum is emphasized, with discussion of cytochrome P-450, mixed function amine oxidase, and peroxidase-dependent reactions. Reduction, further oxidation, N-dealkylation, deamination, rearrangement, acylation and deacylation, and miscellaneous reactions of N-oxidized compounds to yield secondary metabolites, some stable and some highly reactive with macromolecular cell constituents, are described. (440 Refs)

44. INDUSTRIAL BLADDER CANCER.

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Consultant Urologist, Royal Infirmary, Huddersfield HD3 3EA, England
Br Med J; 284(6316):614-615 1982

Incidence, history, industrial screening, and compensation for occupational bladder cancer are discussed. Past research indicated that exposure to benzidine, beta- or alpha- napthylamine increased the risk of dying from bladder cancer. Regular screening of workers is recommended since reversal of early cases is possible with intravesical doxorubicin therapy. Legislation to compensate workers who develop bladder cancer should be revised to include compensation for early disease, since carcinoma in situ usually occurs before the actual development of a tumor, and to include more people. (17 Refs)

45. EFFECT OF HEAT SHOCK ON POLY(ADP-RIBOSE) SYNTHETASE AND DNA REPAIR IN DROSOPHILA CELLS.

Nolan NL, Kidwell WR
Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205
Radiat Res; 90(1):187-203 1982

The capacity of Drosophila cells to repair gamma-ray induced DNA lesions using the quantity of poly(ADP-ribose) synthetase (PARS) left after heat shock (37 C) was investigated. PARS was not necessary for rejoining gamma-ray induced DNA strand breaks. Inhibitors of PARS, 3-aminobenzamide and 5-methyl nicotinamide, lowered the PARS level in whole cells and prevented an increase in polymer levels following irradiation, without blocking the rejoining of gamma-ray-induced DNA strand breaks. (58 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
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6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 0 6510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.
Melton CE
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Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
Chu KC, Milman HA
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Environ Health Perspect; 41:211-220 1981

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11. ALCOHOL AND CANCER.
MacSween RN
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Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
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Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
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Banbury Rep; 7:71-81 1981

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15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
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16. THE MEANING OF CANCER 'DIETS'.
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17. RISK FACTORS FOR CERVICAL CANCER.
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21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
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Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):179-202 1981

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Lockey JE
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

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Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
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Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

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26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
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Pathol Biol (Paris); 30(2):117-123 1982
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Hartung J
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J Theor Biol; 94(1):173-178 1982

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Anisimov VN
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29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
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31. ONCOGENES.
Bishop JM
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Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
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Scully C
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Oral Surg; 53(2):157-169 1982

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34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
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35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
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Watson DH, Lindsay DG
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J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.

Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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CHEMICAL CARCINOGENESIS

Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/09

SEPTEMBER, 1982

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ANILINES AND EXTENDED ANILINES

1. POLY(ADENOSINEDIPHOSPHORIBOSE) POLYMERASE INHIBITORS STIMULATE UNSCHEDULED DEOXYRIBONUCLEIC ACID SYNTHESIS IN NORMAL HUMAN LYMPHOCYTES.

Sims JL, Sikorski GW, Catino DM, Berger SJ, Berger NA
(c/o N. A. Berger) Hematology/Oncology Div., Dept. Medicine, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
Biochemistry; 21(8):1813-1821 1982

Thirty-three analogues of the nicotinamide and adenine portions of NAD+ were evaluated for (1) their effectiveness as inhibitors of poly(adenosinediphosphoribose) polymerase in nucleotide permeable lymphocytes, (2) their ability to interfere with NAD+ lowering in DNA-damaged cells, (3) their ability to inhibit accumulation of poly(adenosinediphosphoribose) in DNA-damaged cells, and (4) their ability to stimulate unscheduled DNA synthesis in DNA-damaged cells. Poly(adenosinediphosphoribose) polymerase was effectively inhibited by six-membered aromatic ring compounds containing a carboxamide group such as nicotinamide, picolinamide, 5-methylnicotinamide, benzamide, 3-aminobenzamide, and 5-methoxy-

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benzamide. Compounds containing a carboxylic acid group rather than a carboxamide group did not inhibit poly(adenosinediphosphoribose) polymerase. Purine analogues such as theobromine and theophylline were also effective inhibitors of poly(adenosinediphosphoribose) polymerase. The ability of these compounds to inhibit poly(adenosinediphosphoribose) polymerase in nucleotide permeable cells correlated with their ability to retard NAD+ lowering in vivo in cells treated with N-methyl-N'-nitro-N-nitrosoguanidine. However, the most effective polymerase inhibitors caused the greatest retardation in the rate of NAD+ lowering. The compounds that were the most effective polymerase inhibitors in vitro were also the most potent in retarding NAD+ lowering in vivo and the most potent in delaying poly(adenosinediphosphoribose) accumulation in vivo. These compounds were also found to be the most effective stimulators of unscheduled DNA synthesis. For example, unscheduled DNA synthesis in UV-irradiated cells was stimulated two-fold by treatment with 2 mM benzamide, nicotinamide, or 3-aminobenzamide. (24 Refs)

2. INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN RAT HEPATOCYTES FOLLOWING IN VIVO TREATMENT WITH DINITROTOLUENE.

Mirsalis JC, Butterworth BE
SRI International, Building 205, 333 Ravenswood Ave., Menlo Park, CA, 94025
Carcinogenesis; 3(3):241-245 1982

The purpose of this study was to examine the induction of unscheduled DNA synthesis (UDS) by the potent hepatocarcinogen technical grade dinitrotoluene (tgDNT; 76% 2,4-dinitrotolulene, 19% 2,6-dinitrotolulene) using the in vivo-in vitro hepatocyte DNA repair assay. Male Fischer-344 rats were treated by gavage and hepatocytes were isolated by liver perfusion and cultured with [3H]thymidine. UDS was measured by quantitative autoradiography as net grains/nucleus (NG); greater than or equal to NG was considered positive. Controls consistently had-3 to-6 NG. A dose-related increase in UDS was observed 12 hr after treatment, with 200 mg/kg tgDNT producing 26 NG. A 50-fold increase in the number of cells in S-phase was observed at 48 hr after treatment. This increase in S-phase cells could be suppressed in the presence of 10-20 mM hydroxyurea (HU), while the same levels of HU did not affect the level of UDS at 12 hr after treatment. 2,4-DNT produced only a weak response, in contrast to 2,6-DNT which was a potent inducer of UDS. Treatment of female rats with tgDNT yielded only modest increases in UDS and DNA replication relative to males. These results are consistent with the carcinogenicity studies and indicate that tgDNT is a potent genotoxic agent, with 2,6-DNT contributing the major portion of the effect. (Author abstract) (20 Refs)

3. MUTAGENICITY IN SALMONELLA TYPHIMURIUM AND STRUCTURE-ACTIVITY RELATIONSHIPS OF WASTEWATER COMPONENTS EMANATING FROM THE MANUFACTURE OF TRINITROTOLUENE.

Spanggord RJ, Mortelmans KE, Griffin AF, Simmon VF
SRI International, Menlo Park, CA, 94025
Environ Mutagen; 4(2):163-179 1982

Mutagenic screening of 36 polynitroaromatic compounds in wastewater of a plant that manufactures 2,4,6-trinitrotoluene (TNT) was accomplished with strains TA1535, TA1537, TA1538, TA98, and TA100 of Salmonella typhimurium using the Ames test with and without microsome S-9 mix from Sprague-Dawley rats. Five dose levels ranging up to 5,000 ug/plate were used. Combinations of the wastewater components to yield a synthetic condensate blend were mutagenic in all 5 strains with and without metabolic metabolic activation. The most active compounds as determined by mutagenic potency with strain TA100 were 2,4,5-TNT greater than 3,5-dinitroaniline greater than 1,3,5-trinitrobenzene, which occur as trace elements in the discharge from munitions production facilities. The three components represent 0.6% of the waste, but account for approx 20% of the mutagenic potency of the wastewater. Over 80% of the compounds tested were mutagenic in either strain TA98 or TA100. Generally compounds showing activity with or without S-9 were more mutagenic in the absence of metabolic activation. Mutagenicity of polynitroaromatic compounds in S typhimurium depends primarily on the nitroreductase activity of the strains; enzymatic reduction is favored by para orientation of nitro groups in TNTs, aminodinitrotoluenes, and dinitrotoluenes. (20 Refs)

4. INHIBITION OF HUMAN TUMOUR CLONOGENICITY BY CHLORAMBUCIL AND ITS METABOLITES.

Goodman GE, McLean A, Alberts DS, Chang SY
(c/o Alberts) Hematology/Oncology Section, Univ. Arizona Health Sciences Center, Tuscon, AZ, 85724
Br J Cancer; 45(4):621-623 1982

The in vitro anticancer activity of chlorambucil (CHL) and its major metabolites was examined in a soft-agar cloning system. Two human cell lines were used for drug testing: the RPMI 8226 myeloma line and the Hec 1A endometrial-carcinoma line. CHL, phenylacetic acid mustard (PAAM, the major plasma metabolite), and dehydrochlorambucil (DCHL) had similar activities, as determined in a simplified two-layer soft-agar cloning system and the 8226 cell line, showing 70% inhibition of colony formation at concentrations between 2 and 4 ug/ml. 2[4-N-(2-chloroethyl)aminophenyl]acetic acid was less active, requiring 20 ug/ml to achieve 80% inhibition of colony formation. Using the Hec 1A cell lines, 3-8 ug/ml of CHL, PAAM, and DHCL were required to achieve 70% inhibition of colony formation. Again, the monochloroethyl metabolite was less active, producing 30% inhibition of colony formation at a concentration of 20 ug/ml. The results indicated that CHL and its two bifunctional alkylating metabolites, PAAM and CHL, have similar inhibitory effects on colony forming units of two neoplastic human cell lines. The monofunctional alkylating metabolite was less active, requiring 10-20-fold drug concentrations to produce comparable inhibition of colony forming units. (6 Refs)

5. DNA DAMAGE IN LIVER, KIDNEY, BONE MARROW, AND SPLEEN OF RATS AND MICE TREATED WITH COMMERCIAL AND PURIFIED ANILINE AS DETERMINED BY ALKALINE ELUTION ASSAY AND SISTER CHROMATID EXCHANGE INDUCTION.

Parodi S, Pala M, Russo P, Zunino A, Balbi C, Albini A, Valerio F, Cimberle MR, Santi L
Dept. Oncology, Istituto Scientifico per lo Studio e la Cura dei Tumori, 16132 Genoa, Italy
Cancer Res; 42(6):2277-2283 1982

Aniline of unknown purity has been reported to induce spleen hemangiosarcoma in rats. Aniline has been found to be negative in terms of mutagenicity in both bacteria and yeasts. We have found that both commercial (already rather pure) and repurified aniline are clearly positive to a similar extent in inducing DNA damage in vivo in liver and kidney of rats. Both the commercial and repurified product are also clearly positive in induction of sister chromatid exchanges in vivo in male Swiss mice bone marrow cells. Liver, kidney, and bone marrow DNA damage was absent in male Swiss mice. (Author abstract) (30 Refs)

6. PROSTATE ADENOCARCINOMA IN RATS: INDUCTION BY 3,2'-DIMETHYL-4-AMINOBIPHENYL.

Katayama S, Fiala E, Reddy BS, Rivenson A, Silverman J, Williams GM, Weisburger JH
(c/o Weisburger) American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
JNCI; 68(5):867-873 1982

Five experiments designed for various purposes [mainly for the study of colon carcinogenesis in inbred F344 male rats given sc injections of 3,2'-dimethyl-4-aminobiphenyl (DMAB)] were reviewed as to the production and presence of neoplastic lesions of the prostate gland. The overall incidence of prostate proliferative lesions among 239 animals exposed to DMAB was 32% (95 animals). Early in situ carcinomas were present in 6 animals, larger intra-acinar carcinomas in situ in 28, and invasive carcinoma in 1. None of the control animals in these studies exhibited prostate neoplasms. The conclusion, therefore, is that DMAB can induce adenocarcinomas in the rat prostate gland. (Author abstract) (49 Refs)

7. INHIBITION OF DNA SYNTHESIS AND ALTERATION TO DNA STRUCTURE BY THE PHENACETIN ANALOG P-AMINOPHENOL.

Hayward NK, Lavin MF, Craswell PW
(c/o Lavin) Dept. Biochemistry, Univ. Queensland, Brisbane 4067, Australia
Biochem Pharmacol; 31(7):1425-1429 1982

p-Aminophenol a structural analog and minor metabolite of phenacetin has previously been shown to be a potent nephrotoxic agent. In this report we have shown that p-aminophenol has a marked effect on DNA function and structure. DNA synthesis was inhibited in a dose-dependent manner in human lymphoblastoid cells after exposure to p-aminophenol. Results suggest that DNA synthesis is inhibited by the action of p-aminophenol on DNA structure. At low concentrations of p-aminophenol a reduction in the degree of supercoiling of cellular DNA is observed, as determined by sedimentation under neutral conditions. However at higher concentrations an increase in sedimentation of nucleoids (supercoiled molecules) is obtained which is indicative of an increased level of supercoiling or a more compact structural form of DNA due to folding or aggregation. The number of single strand breaks in DNA, when determined by sedimentation in alkaline sucrose gradients, increases with increasing dose of p-aminophenol. The increase in strand breakage observed at lower concentrations of p-aminophenol agrees with the reduced sedimentation rate obtained under neutral conditions. At higher concentrations of p-aminophenol the extent of breakage of DNA increases under alkaline conditions but an increase in sedimentation occurs under neutral conditions. (Author abstract) (23 Refs)

8. MUTAGENICITY OF 4,4'-METHYLENEDIANILINE DERIVATIVES IN THE SALMONELLA HISTIDINE REVERSION ASSAY.

Rao TK, Dorsey GF, Allen BE, Epler JL
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Arch Toxicol; 49(3/4):185-190 1982

The compound 4,4'-methylenedianiline and its derivatives were assayed for mutagenicity in the Salmonella/microsomal mutagenicity assay developed by Ames. A specificity to revert strain TA98 suggests a mechanism of frameshift mutagenesis. Liver microsomal preparations (S-9) from rats induced with phenobarbital were most effective for metabolic activation. Alkyl substitution of 4,4'-methylenedianiline did not alter its mutagenic activity; however, substitution of both positions ortho to the amino group eliminated mutagenic activity. Substitution with alkoxy-carbonyl groups eliminated mutagenic activity, whereas halogen substitution (chlorine, fluorine) enhanced the mutagenicity activity. The results presented here show the use of structure-activity studies as predictive tools for the assessment of genotoxic properties of industrial chemicals. (Author abstract) (14 Refs)

9. INHIBITION OF MICROSOMAL DRUG OXIDATIONS BY ALIPHATIC HALOHYDROCARBONS: CORRELATION WITH VAPOUR PRESSURE.

Poplawski-Tabarelli S, Uehleke H
(c/o Uehleke) Dept. Toxicology, Federal German Health Office (Bundesgesundheitsamt), D-1000 Berlin 33, W. Germany
Xenobiotica; 12(1):55-61 1982

The effects of 12 halogenated aliphatic compounds on microsomal N-dealkylation, C-hydroxylation and N-oxidation of N-methylaniline and N-hydroxylation of p-chloroaniline were determined in closed reaction vessels. There is no correlation between the volatility of the agents investigated and their binding characteristics to oxidized or reduced microsomal cytochrome P-450. High correlation was observed between inhibition of cytochrome P-450-mediated drug oxidations and the boiling points (vapor pressure) of the individual compounds. The N-oxidation of N-methylaniline, which is not catalyzed by cytochrome P-450, did not show this correlation. Other factors eg ligand formation with reduced cytochrome P-450, lipid peroxidation and heme destruction, production of carbon monoxide, and alterations of microsomal cofactors, did not produce significant inhibition. Many artefacts occur when reaction velocities, inhibition constants and optical affinities to microsomal cytochromes are determined for volatile chemicals under uncontrolled conditions. (Author abstract) (29 Refs)

10. COMPARISON OF THE MUTAGENICITIES OF 4-AMINOBIPHENYL AND BENZIDINE IN THE SALMONELLA/MICROSOME, SALMONELLA/HEPATOCYTE AND HOST-MEDIATED ASSAYS.

Bos RP, Van Doorn R, Yih-van de Hurk E, Van Gemert PJ, Henderson PT
Inst. Pharmacology and Toxicology, Faculty Medicine, Univ. Nijmegen, Nijmegen, The Netherlands
Mutat Res; 93(2):317-325 1982

The mutagenicity of two structurally related carcinogenic aryl amines, 4-aminobiphenyl (4-AB) and benzidine (BZ), which are subject to a complex in vivo metabolism, was studied by three different test methods. The Salmonella/microsome (S/m) assay was performed by the Ames method with strains TA1538 and TA100 of Salmonella typhimurium. In the Salmonella intrasanguineous assay, male Wistar rats (200 g) were injected in the lateral tail vein with 1 ml of saline suspension of S typhimurium, followed by ip injection of either 4-AB or BZ. Revertants in bacteria grown from liver suspensions were counted. The Salmonella/hepatocyte (S/h) assay involved counting of revertant colonies after plating from an incubation mixture containing rat liver hepatocytes, S typhimurium, and mutagen incubated at 37 C for 1 hr. The mutagenicity of the two compounds varied depending upon whether metabolic inactivation was carried on in vivo or by S9 mix in the Ames test. The results obtained for both compounds in the S/h assay resembled more closely those of the host-mediated assay than they did the results of the S/m assay. (16 Refs)

11. ENHANCEMENT OF ULTRAVIOLET OR N-METHYL-N'-NITRO-N-NITROSOGUANIDINE SENSITIVITY OF DICTYOSTELIUM DISCOIDEUM BY 3-AMINOBENZAMIDE.

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Molecular and Cell Biology Program, 201 Althous Lab., Pennsylvania State Univ., University Park, PA, 16802

Photochem Photobiol; 35(4):515-519 1982

The amoeboid cells of Dictyostelium discoideum NC-4 possess a 3-aminobenzamide(3-ABA)-sensitive repair mechanism for DNA damages induced by UV-irradiation or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-treatment. We have studied the effect of 3-ABA on each step of excision repair in the UV-irradiated cells. Although the nicking of DNA-strand and the excision of pyrimidine dimers are insensitive to 3-ABA, the rejoining of DNA strand-breaks is sensitive. The frequency of mutation induced by UV-irradiation or MNNG-treatment is depressed by 3-ABA. The mechanisms of repair inhibition by 3-ABA are discussed. (Author abstract) (24 Refs)

12. SCE INDUCTION IN HUMAN LYMPHOCYTES BY COMBINED TREATMENT WITH ANILINE AND NORHARMAN.

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Dept. Biology, Keio Univ., Yokohama 223, Japan

Mutat Res; 101(2):165-172 1982

The ability of aniline (AN) and norharman (NH) to induce an increase in the number of sister chromatid exchanges (SCE) was examined in peripheral blood lymphocytes from normal healthy males. After a 24 hr exposure of lymphocytes to AL (2 x 10(-3) and 10(-2) M) a very slight increase in SCE frequency was observed. After 48-hr AN treatments (10(-2) M), few if any cells were found at second mitosis. At 10(-3) and 10(-4) M AN concentrations, an increase in SCE was not apparent. Treatment with the AN metabolite p-aminophenol (10(-4) M) increased the yield of SCE. Addition of S9 mix did not result in increased SCE. Treatment of lymphocytes with AN plus NH in the presence of S9 mix increased SCE frequencies. NH plus S9 also induced an increase in SCE. The incidence of SCE decreased with increasing concentrations of AN in treatments with AN, NH, and S9 combined. Thus, AN seemed to counteract the SCE-inducing activity of activated NH. The frequency of NH-induced SCE was dose-dependent and increased with increasing concentrations of S9. Simultaneous application of NH and AN for 48 hr did not affect the NH-induced SCE frequencies. The results indicated that the addition of NH, which enhances the sensitivity of the Salmonella/microsome test, does not produce an enhancement of the sensitivity of the SCE test. (13 Refs)

13. THE CARCINOGENIC EFFECT OF AROMATIC AMINES: AN EPIDEMIOLOGICAL STUDY ON THE ROLE OF O-TOLUIDINE AND 4,4'-METHYLENE BIS(2-METHYLANILINE) IN INDUCING BLADDER CANCER IN MAN.

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Inst. Occupational Health, Turin Univ., CTO- Via Zuretti, 29-10126 Torino, Italy

Environ Res; 27(2):241-254 1982

Cause-specific mortality of 906 workers first employed 1922-1970 in a dyestuff factory in Northern Italy was compared to national figures; a marked excess of bladder cancer was observed (36 observed vs 1.23 expected deaths). The mean latent period was 25 years. The excess was higher among those with longer duration of exposure. Some excess of mortality from lung cancer, laryngeal cancer, and esophageal cancer was also found, but a clear explanation could not be provided regarding the causal role of aromatic amines. Mortality from bladder cancer was very much higher among those exposed in benzidine and naphthylamines manufacture as compared to those only exposed in use or intermittent contact. Excess bladder cancer was also very high among workers in fuchsin manufacture. There is evidence that O-toluidine and 4,4'-methylene bis(2-methylaniline) should be implicated in such excess mortality. Caution in handling these compounds is therefore suggested and the need for further studies to confirm such findings is stressed. (Author abstract) (19 Refs)

14. A STUDY OF AROMATIC NITRO COMPOUNDS FOR THE SELECTION OF CANDIDATES FOR CARCINOGEN BIOASSAY.

Helmes CT, Fung VA, Lewin B, McCaleb KE, Malko S, Pawlovich AM

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J Environ Sci Health [A]; 17(1):75-128 1982

The class of aromatic nitro compounds was studied in order to nominate chemicals to the National Cancer Institute as candidates for carcinogen bioassay. Scope was defined as commercially significant organic compounds that contain an aromatic, six-membered carbocyclic system with at least one direct substitution of the nitro (NO2) functionality. Potential carcinogenicity was evaluated from published reports. After application of several qualifying criteria relating to previous, current, or planned carcinogenicity tests and to commercial significance, a preliminary candidate list of 441 chemicals was reduced to 210 chemicals. Based upon consideration of both the suspicion of possible carcinogenic activity and evidence indicating potential exposure, the following 14 chemicals were nominated: 4-chloro-2-nitroaniline, 2,4-dinitroaniline, 4-nitroaniline, benefin, 2-bromo-4,6-dinitroaniline, 2-nitroanisole, nitrobenzene, 4,4'-dinitro-1,1'-stilbenedisulfonic acid, 1,8-dihydroxy-4,5-dinitroanthraquinone, C.I. Pigment Red 3, C.I. Pigment Orange 5, C.I. Pigment Red 23, C.I. Pigment Yellow 74, and 2-amino-6-nitrobenzothiazole. (54 Refs)

FLUORENAMINES: IN VIVO

15. DETECTION OF N-HYDROXY-2-ACETYLAMINOFLUORENE - DNA ADDUCTS IN RAT LIVER MEASURED BY RADIOIMMUNOASSAY.

Rio P, Bazgar S, Leng M
Centre de Biophysique Moleculaire, CNRS, 1A, Avenue de la Recherche Scientifique, 45045 Orleans Cedex, France
Carcinogenesis; 3(2):225-227 1982

Antibodies to imidazole ring opened derivatives of alkali treated N-(guanosin-8-yl)-2-aminofluorene (1-[6-(2,5-diamino-4-oxopyrimidinyl-N(6)-riboside)]-3 (2-fluorenyl)urea) were elicited in rabbits by immunization with a conjugate between the ring-opened derivative and bovine serum albumin. The specificity of the antibodies was studied by radioimmunoassay. These antibodies and antibodies to N-(guanosin-8-yl)-N-acetyl-2-aminofluorene were used to titrate the adducts formed in liver DNA of rats treated with N-hydroxy-2-acetylaminofluorene. The ring-opened derivates represent approx 10% of the dGuo-C8-adducts. (Author abstract) (18 Refs)

16. THYROID ACTIVITY DURING HEPATOCARCINOGENESIS BY N-2-FLUORENYLACETAMIDE IN THE MALE RAT.

Aussel C, Lafaurie M, Castelli D, Formento JL, Stora C
Laboratoire d'Histologie et d'Immunologie, INSERM U210, 06034 Nice Cedex, France
Res Commun Chem Pathol Pharmacol; 36(1):105-117 1982

During chemical hepatocarcinogenesis by N-2-fluorenylacetamide, the hormonal status of male Sprague Dawley rats is modified. The histological study of the thyroid gland demonstrates a decreased activity evidenced by an augmentation of the follicle size and a reduced size of follicular epithelium. The level of T3 and T4 reflects in part this decreased activity. Comparison with female rats treated in the same conditions shows an opposite effect of N-2-fluorenylacetamide. Indeed in the female, the thyroid gland presented an hyperactive state accompanied by a drastic decrease of serum T3 and T4. This difference in thyroid activity might take an important part in the mechanism responsible for the sex difference in liver cancer induction by N-2-fluorenylacetamide. (Author abstract) (19 Refs)

17. ORGAN-SPECIFIC PROMOTING EFFECTS OF PHENOBARBITAL SODIUM AND SODIUM SACCHARIN IN THE INDUCTION OF LIVER AND URINARY BLADDER TUMORS IN MALE F344 RATS.

Nakanishi K, Fukushima S, Hagiwara A, Tamano S, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizucho-cho, Mizuho-ku, Nagoya 467, Japan
JNCI; 68(3):497-500 1982

Studies were conducted to determine whether initial treatment with N-2-fluorenylacetamide (2-FAA) or N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) followed by treatment with either phenobarbital sodium (PB) or sodium saccharin (SS) induced or enhanced liver and/or bladder tumorigenesis. Male inbred F344 rats were given 0.05% PB and 5.0% SS in the diet for 32 wk after 4-wk administration of 0.02% 2-FAA or 0.01% BBN. PB significantly enhanced hepatocarcinogenesis after 2-FAA treatment and induced hyperplastic liver nodules after BBN treatment. The SS significantly enhanced induction of bladder hyperplasias, but not papilloma after BBN treatment, and induced bladder hyperplasias after 2-FAA treatment. However, PB had no effect on the bladder and SS had no effect on the liver after either 2-FAA or BBN treatment. The data indicate that although 2-FAA and BBN have tumor-initiating effects in the liver and urinary bladder, the tumor-promoting effects of PB and SS are organ-specific. The tumor-promoting effect of PB for the liver is relatively greater than that of SS for the urinary bladder. (Author abstract) (25 Refs)

18. RAT MAMMARY GLAND CARCINOGENESIS AFTER LOCAL INJECTION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES: RELATIONSHIP TO METABOLIC ACTIVATION.

Allaben WT, Weeks CE, Weis CC, Burger GT, King CM
Div. Carcinogenesis, Natl. Center Toxicological Res., HFT-110, Jefferson, AR, 72079
Carcinogenesis; 3(3):233-240 1982

A single local injection of 2.5 umol of N-hydroxy-N-formyl-2-aminofluorene (N-hydroxy-FAF), N-hydroxy-N-acetyl-2-aminofluorene (N-hydroxy-AAF), or N-hydroxy-N-propionyl-2-aminofluorene (N-hydroxy-PAF) to each of the six left mammary glands of female Sprague-Dawley derived CD rats gave a mammary tumor incidence, after 12 mo, of 53% for the N-acetyl 41% for the N-formyl and 33% for the N-propionyl derivatives of N-hydroxyl-N-2 aminofluorene When N-acetyl-2-aminofluorene (AAF) was applied as above there was only an 8% mammary tumor incidence. Arylhydroxamic acid N,O-acyltransferase activity has been demonstrated in the mammary glands of male, and lactating and non-lactating female Sprague-Dawley derived CD rats by means of a nucleic acid binding assay. Mammary gland cytosol catalyzed tRNA adduct formation to a greater extent with N-hydroxy-FAF. AAF was not activated by this enzyme. Ammonium sulfate fractionation demonstrated the presence of two enzymes, one specific for N-hydroxy-FAF, the other specific for N-hydroxy-AAF and N-hydroxy-PAF. Gel filtration chromatography of mammary gland cytosol demonstrated the presence of two enzymes of differing acyl specificity. Mammary gland microsomes catalyzed the formation of tRNA adducts, but only with the N-hydroxy-FAF derivative. Assays that tested the mutagenic potential of the arylhydroxamic acids in Salmonella typhimurium TA-1538 with either mammary gland cytosol or microsomes demonstrated the order of mutagenicity to be N-hydroxy-FAF much greater than N-hydroxy-AAF greater than N-hydroxy-PAF. A similar order of mutagenicity was demonstrated without an external metabolic activation system. These data demonstrate the presence of two distinct enzymes in the rat mammary gland that activate arylhydroxamic acids. (37 Refs)

19. IDENTIFICATION OF GLUTATHIONE CONJUGATES FORMED FROM N-HYDROXY-2-ACETYLAMINOFLUORENE IN THE RAT.

Meerman JH, Beland FA, Ketterer B, Srai SK, Bruins AP, Mulder GJ
Dept. Pharmacology, State Univ. Groningen, Bloemsingel 1, 9713 BZ Groningen, The Netherlands
Chem Biol Interact; 39(2):149-168 1982

Rats which had received N-hydroxy-2-acetylaminofluorene (N-OH-AAF) excreted two glutathione conjugates in the bile. Pretreatment with the sulfotransferase inhibitor pentachlorophenol reduced the amounts excreted by 50% suggesting that these conjugates were formed in vivo from the highly reactive N-O-sulfate ester of N-OH-AAF (AAF-N-sulfate). In order to identify these biliary conjugates synthetic GSH conjugates were prepared by the reaction of N-acetoxy-AAF, (a model compound for AAF-N-sulfate), with GSH. Four conjugates were isolated and characterized by ultraviolet, proton magnetic resonance, mass spectroscopy and by the determination of their amino acid composition. These conjugates were identified as 1-, 3-, 4-and 7-(gluathion-S-yl)-N-acetyl-2-aminofluorene, respectively. The two biliary conjugates were identified as 1-and 3-(glutathion-S-yl)-N-acetyl-2-aminofluorene. (Author abstract) (45 Refs)

FLUORENAMINES: IN VITRO

20. MUTAGENICITY OF N-HYDROXY-2-ACETYLAMINOFLUORENE AND N-HYDROXYPHENACETIN AND THEIR RESPECTIVE DEACETYLATED METABOLITES IN NITROREDUCTASE DEFICIENT SALMONELLA TA98FR AND TA100FR.

Wirth PJ, Alewood P, Calder I, Thorgeirsson SS
Biochemical Pharmacology Section, Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD, 20205
Carcinogenesis; 3(2):167-170 1982

The mutagenicity of N-hydroxy-2-acetylaminofluorene and N-hydroxyphenacetin and their respective deacetylated metabolites, N-hydroxy-2-aminofluorene and 2-nitrosofluorene, and N-hydroxyphenetidine and p-nitrosophenetole was determined in nitroreductase deficient Salmonella tester strains TA98FR and TA100FR. The mutagenicity of N-hydroxy-2-acetylaminofluorene mediated by either rat liver microsomes or rat liver 105,000 g supernatant fractions was no different in either TA98 (nitroreductase proficient) or TA98FR (nitroreductase deficient). Similarly the mutagenicity of N-hydroxyphenacetin mediated by hamster liver microsomes was not affected by either the presence or absence of nitroreductase activity in TA100. N-Hydroxy-2-aminofluorene and 2-nitrosofluorene were equipotent direct acting mutagens in both TA98 and TA98FR, as were both N-hydroxyphenetidine and p-nitrosophenetole in TA100 and TA100FR. Ascorbate (5 mM) and NADPH (1 mM) had no significant effect on the mutagenicity of either N-hydroxy-2-acetylaminofluorene, N-hydroxy-2-aminofluorene, or 2-nitrosofluorene in TA98 or TA98FR whereas ascorbate and NADPH markedly inhibited the mutagenicity of both N-hydroxyphenetidine and p-nitrosophenetole in both TA100 and TA100FR. Ascorbate appears to be inhibiting the mutagenicity of N-hydroxyphenetidine and p-nitrosophenetole as a result of the nonenzymatic chemical reduction of these compounds to non-mutagenic derivatives. (Author abstract) (15 Refs)

21. POTENT MUTAGENIC IMPURITIES IN A COMMERCIAL SAMPLE OF 3-NITRO-9-FLUORENONE.

Jin ZL, Xu XB, Nachtman JP, Wei ET
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Cancer Lett; 15(3):209-214 1982

Potent mutagenic impurities were detected in a commercial sample of 3-nitro-9-fluorenone (NFN); characterization of these impurities by high pressure liquid chromatography (HPLC) and high-resolution mass spectrometry (HRMS) is reported. Several peaks were noted in the HPLC chromatogram of NFN, indicating that the impurities were present. When tested for mutagenicity in the Ames Salmonella assay, Fractions II, III, IV, and V were active. Fraction II accounted for 88% of the mass but its specific activity was at least 20x less than that of Fractions III and V. HRMS revealed the accurate masses of these fractions. Fraction II was a mononitrofluorenone. Fraction III and V yielded molecular ion peaks and fragmentation patterns of structures corresponding to a dinitrofluorenone and an acetamidomononitrofluorenone. Two commercially available standards, 2,7-dinitro-9-fluorenone (DNFN) and 2-acetamido-3-nitro-9-fluorenone (ANFN), were used for comparing with the unknown fractions. The HPLC retention time of DNFN was practically the same as that of Fraction III and that of ANFN was close to that of Fraction V. The mutagenic activities of DNFN and ANFN were also similar to the activities of the corresponding Fractions III and V: 0.10-0.22 ug of each chemical yielded 1,000 TA98 revertants in the linear region of the does-response correlation. Fraction IV yielded a compound with an accurate mass and fragmentation pattern similar to xanthone (XT). XT was not mutagenic in the TA98 assay when tested at doses up to 10 ug/plate. (14 Refs)

22. RECONSTITUTION OF RODS FROM TOBACCO MOSAIC VIRUS PROTEIN AND RNA MODIFIED WITH BULKY CARCINOGENS.

Fraenkel-Conrat H, Singer B, Yakanami Y, Santella RM, Grunberger D
Central Res. Inst., Japan Tobacco and Salt Public Corporation, 6-2, Umegaoka, Midori-ku, Yokohama 227, Japan
Proc Natl Acad Sci USA; 79(8,part1):2541-2543 1982

Tobacco mosaic virus (TMV) RNA was treated with radioactive N-acetoxy-2-acetylaminofluorene (N-acetoxy-AAF) and (+/-)-7beta, 8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo [alpha]pyrene (BaP diol epoxide) to obtain 3-25 adducts per molecule. Modified full length 30S RNAs and unmodified RNA were reconstituted for various time periods with TMV protein. The particulate products were separated by ultracentrifugation, and the amounts of virus-like material were quantitated by UV spectrophotometry. The length distribution and general appearance of the virus-like rods were studied by electron microscopy. Neither type of carcinogen prevented typical rod formation, but the rate of formation and the maximal yield of reconstituted particles diminished with increasing modification by both agents. The rod length distribution also showed progressively lesser numbers of full-length virus rods. The particulate material contained approximately the same number of adducts as the modified RNA. Thus, it appears that these carcinogen modifications of guanine residues at the N-2 or C-8 atoms did not prevent orderly protein assembly on the RNA but instead slowed up this process and frequently stopped it, possibly at sites where adducts happen to be clustered. (Author abstract) (10 Refs)

23. ANALYSIS OF N-ACETOXY-N-2-ACETYLAMINOFLUORENE-INDUCED FRAME-SHIFTS IN PBR322.

Yoon K, Shelegedin VN, Kallenbach NR
Center Oral Health Res., Sch. Dental Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Mutat Res; 93(2):273-283 1982

A simple system is described which can be used to study directly the sequence change and cellular functions involved in frame-shift mutagenesis by covalently reactive mutagen. Positive and negative alterations in the number of base pairs of tetracycline resistant gene of pBR322, were created by cutting with Sal restriction enzyme followed by either removal with nuclease Sl or extension with reverse transcriptase, and reclosing by a 'blunt-ended' joining reaction catalyzed by T4 DNA ligase. Mutagenesis in vitro by exposure to N-acetoxy-N-2-acetylaminofluorene (AAAF) was used to cause reversion of frame-shifted plasmid molecules. Transformation of AAAF-reacted frame-shift plasmid DNA into Escherichia coli strains AB1157, AB1886, and AB2463 was performed, and a number of revertants (ApRTcR) not represented in unreacted controls were generated. Differential inactivation of the AP gene was observed among the E coli strains. The system used here is suitable for any chemicals that bind covalently to DNA. (25 Refs)

24. RING- AND N-HYDROXYLATION OF 2-ACETYLAMINOFLUORENE BY RECONSTITUTED MOUSE LIVER MICROSOMAL CYTOCHROME P-450 ENZYME SYSTEM.

Lotlikar PD, Wang TF
Dept. Biochemistry, Temple Univ. Medical Sch., Philadelphia, PA, 19140
Toxicol Lett; 11(1/2):173-179 1982

Ring and N-hydroxylation of 2-acetylaminofluorene with partially purified cytochrome P-450 and NADPH-cytochrome c reductase fractions from control and 3-methylcholanthrene (MC)-pretreated mice was investigated. MC pretreated mice produced a severalfold increase in both N- and ring hydroxylations. The specificity of N- and ring hydroxylation lies with the cytochrome P-450 fraction; the one obtained from MC-treated animals being more active than that from controls. (23 Refs)

OTHER FUSED RING AMINES

25. BIOLOGICALLY ACTIVE AROMATIC AMINES DERIVED FROM CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS: SYNTHESIS AND MUTAGENICITY OF AMINOBENZO(A)PYRENES.

Fu PP, Heflich RH, Casciano DA, Huang AY, Trie WM, Kadlubar FF, Beland FA
Natl. Center for Toxicological Res., Food and Drug Admin., Dept. Health and Human Services, Jefferson, AR, 72079
Mutat Res; 94(1):13-21 1982

The mutagenicities of 6-amino-benzo(a)pyrene (6-NH2-BP), three K-region NH2-BPs (4-amino-benzo(a)pyrene, 11-amino-benzo(a)pyrene and 12-amino-benzo(a)pyrene), and two N,N-diacetyl derivatives, (4-N(acetyl)-2-benzo(a)pyrene and 12-N(acetyl)2-benzo(a)pyrene) were examined in the Ames' tester strains TA 1535, TA 1538, TA98 and TA100 and compared to those of the parent compound, benzo(a)pyrene (BP), and of 2-aminofluorene (AF). In the absence of S9 activation only 6-NH2-BP and high doses of AF induced revertants and only in the tester strains sensitive to frameshift mutagens. In the presence of S9, all the compounds were active in TA100, TA98, and TA1538, but none were mutagenic in TA1535. A dose response was observed for each compound. The N,N-diacetyl derivatives were less mutagenic than their parent amines. At high concentrations, however, there was a decrease in mutagenicity for 4-and 12-NH2-BP which was not found with the diacetyl derivatives. The 4-substituted analogues were clearly the most mutagenic in TA98, with a general order of mutagenicity of 4-NH2-BP greater than 4-N(Ac)2-BP greater than 12-NH2-BP greater than 12-N(Ac)2-BP greater than AF greater than 11-NH2-BP approx = BP greater than 6-NH2-BP. The 4-NH2-BP derivatives were also the most active in TA100. While paraoxon had no effect on the overall activity of 4-NH2-BP in either strain, it did decrease the mutagenicity of 4-N(Ac)2-BP by 75%. These data suggest that arylamines derived from carcinogenic polycyclic aromatic hydrocarbons are activated to potent mutagens primarily through S9-mediated metabolism of the parent amine. (13 Refs)

26. HEPATIC MICROSOMAL METABOLISM AND MACROMOLECULAR BINDING OF THE ANTIOXIDANT, N-PHENYL-2-NAPHTHYLAMINE.

Anderson MM, Mitchum RK, Beland FA
(c/o Beland) Natl. Center Toxicological Res., Food and Drug Admin., Jefferson, AR, 72079
Xenobiotica; 12(1):31-43 1982

The hepatic microsomal metabolism of N-phenyl-2-naphthylamine (P2NA), an industrial antioxidant and suspected carcinogen, was studied in seven mammalian species to determine if N-dephenylation, reported to occur in vivo, could be demonstrated in vitro and if macromolecular binding occurs without an obligatory N-dephenylation. The rate of hepatic microsomal metabolism decreased in the order: hamster very much greater than mouse, greater than rat, approx equal to monkey, approx equal to dog, greater than human, approx equal to pig. Metabolism was increased by pretreatment with 3-methylcholanthrene or phenobarbital and decreased by carbon monoxide or 2-[(2,4-dichloro-6-phenyl)phenoxy]-ethylamine, which indicated the involvement of cytochrome P-450 rather than the flavoprotein mixed-function oxidase. All seven species produced two major metabolites identified as 6-hydroxy-P2NA and 4'-hydroxy-P2NA. The carcinogen 2-naphthylamine was not detected in the microsomal incubations. Incubations in the presence of 18O2 indicated that the oxygen incorporated in the products came from molecular oxygen. There was a time-dependent linear increase in covalent binding of P2NA to microsomal protein and the extent of binding approx paralleled the rate of metabolism. Thus, macromolecular binding of this aromatic amine appears to occur without an obligatory N-dephenylation and may be due to the metabolic formation of epoxides. (Author abstract) (31 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

27. EARLY CHANGES IN MITOCHONDRIAL MONOAMINE OXIDASE ACTIVITY OF RAT LIVER DURING HEPATOCARCINOGENS FEEDING.

Kuroiwa Y, Yoshida T, Yamamoto T
Dept. Biochemical Toxicology, Sch. Pharmaceutical Sciences, Showa Univ., 1-5-8 Hatanodai Shinagawa-ku, Tokyo 142, Japan
Excerpta Med Int Congr Ser; 5640:241-250 1982

The effects of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), 2-acetylamino-fluorene (2-AAF), 2-aminofluorene (2-AF), 2-nitrofluorene (2-NF), and N-hydroxy-2-AAF on mitochondrial monoamine oxidase (MAO) activity of rat liver are reported. Male and female Donryu rats were used. Significant decrease (70%) in MAO-B activity was observed during 3'-Me-DAB feeding. The changed patterns of MAO-B activity are similar to those of rat hepatoma. When rats were fed a diet containing 0.05% 2-AAF, a remarkable decrease of MAO-B activity was observed, while MAO-A activity was not affected. In female rats fed 0.05% 2-AAF diet, MAO-B activity was not changed after 1 wk, but decreased to some extent at 3 and 12 wk after the exposure to the carcinogen. The intensity of the MAO-B activity decrease in female rats was to a lesser extent as compared to that of male rats at each time period. 2-AAF higher concentrations inhibited MAO-B activity when added in vitro, but MAO-A activity was strongly inhibited by addition of 10(-7) M 2-AAF. Each compound of fluorene derivatives tested was administered po at a dose of 200 micro moles/kg daily for 7 days. N-hydroxy-2-AAF and 2-AF decreased MAO-B activity. 2-NF did not show any effect under experimental conditions. Effect of 2-AAF on MAO-B activity was examined in thyroxine-treated and riboflavin-deficient rats. An additive decrease of MAO-B activity was observed in 2-AAF and thyroxine-treated animals as compared to the decrease produced by the separate administration. When rats were fed riboflavin-deficient diet for 2 wk, MAO-B activity was decreased to 60% of the control levels. The decreased activity tended to return to control levels if rats were fed the basal diet again. (27 Refs)

28. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

Abe S, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Faculty Science, Hokkaido Univ., North 10, West 8, Sapporo, Hokkaido 060, Japan
Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

29. CARCINOGENICITY TESTS OF ACETOXYMETHYLPHENYLNITROSAMINE AND BENZENEDIAZONIUM TETRAFLUOROBORATE IN SYRIAN HAMSTERS.

Gold B, Salmasi S
Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Lett; 15(3):289-300 1982

The bioassay of acetoxymethylphenylnitrosamine (AMPhN) and benzenediazonium tetrafluoroborate (BDI-BF4) by sc injection and of BDI-BF4 by gavage in Syrian golden hamster is reported. The LD50 of AMPhN was determined by sc injection of olive oil vehicle to be 134.0 mg/kg and 116.6 mg/kg in females and males, respectively. Animals were injected weekly sc with AMPhN in olive oil at 12.5, 6.25, and 3.13 mg/kg, which corresponded to 1/10, 1/20, and 1/40 av acute LD50. At the two higher doses, animals developed serious sores at the injection site and treatment was terminated after 4 wk for these two dose groups. A lower dose of 1.56 mg/kg was then initiated. Results of the experiment are presented. The acute LD50 of BDI-BF4 in hamsters by sc injection in 0.9% saline was 166.2 mg/kg and 219.2 mg/kg in females and males, respectively. For chronic testing, freshly prepared solutions of BDI-BF4 were injected sc weekly at 19, 9.5, and 4.75 mg/kg. One control group received sc injections of saline solutions and another 11.5 mg/kg of sodium tetrafluoroborate in 0.9% saline, a dose corresponding to the molar equivalent of the highest dose of BDI-BF4 used. At these three doses of BDI-BF4, the hamsters rapidly developed open sores at the injection sites and the treatment was halted after 10 wk. An additional two doses at 2.38 mg/kg and 1.19 mg/kg were started and these animals were treated for life. BDI-BF4 was less toxic by intragastric administration, with the acute LD50 being 353.7 mg/kg for both females and males. No significant qualitative or quantitative difference in tumors was found between treated and control animals in this experiment. (37 Refs)

30. TUMOR PROMOTER STIMULATED IRREVERSIBLE BINDING OF N-METHYLAMINOAZOBENZENE TO POLYMORPHONUCLEAR LEUKOCYTE DNA.

Takanaka K, O'Brien PJ, Tsuruta Y, Rahimtula AD
(c/o Rahimtula) Dept. Biochemistry, Memorial Univ. Newfoundland, St. John's, Newfoundland, Canada
Cancer Lett; 15(3):311-315 1982

The irreversible binding of N-methylaminoazobenzene (MAB) to nuclear DNA catalyzed by guinea pig polymorphonuclear leukocytes (PMN), and the initiation of binding by 12-O-tetradecanoylphorbol-13-acetate (TPA), were studied. A 10(-6) M concentration of TPA resulted in the binding of 43.3 picomole of MAB to the DNA present in 10(7) cells. Little binding occurred in the absence of TPA. The binding was proportional to the number of PMN present. Evidence implicating the involvement of H2O2 is presented. Addition of catalase to the incubation medium reduced DNA binding of MAB by 80%. Addition of superoxide dismutase (which catalyzes the dismutation of O2-to produce H2O2) increased the binding by 30%, suggesting that the rate of H2O2 production was limiting. Addition of horseradish peroxidase (HRP), which has high affinity for H2O2, increased the binding by 75%. Since HRP cannot penetrate the PMN plasma membrane, the activation of MAB by HRP must occur outside the cell itself and the reactive intermediates are apparently sufficiently stable to penetrate the plasma membrane and interact with the DNA. The antioxidant butylated hydroxyanisole reduced the MAB bound to DNA by 90%, suggesting the involvement of free radicals in the activation process. The observation that TPA can trigger the irreversible binding of MAB to DNA suggests that it could also be involved in the initiation process. (18 Refs)

31. ROLE OF ISOZYMES OF CYTOCHROME P-450 IN THE METABOLISM OF N,N-DIMETHYL-4-AMINOAZOBENZENE IN THE RAT.

Levine WG, Lu AY
Dept. Molecular Pharmacology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Drug Metab Dispos; 10(2):102-109 1982

The metabolism of N,N-dimethyl-4-aminoazobenzene (DAB) was investigated in vitro by use of hepatic 10,000g supernatant fraction, microsomes, and purified cytochromes P-450 prepared from rats. Position-selective metabolism was studied in response to induction by 3-methylcholanthrene (MC), phenobarbital (PB), beta-naphthoflavone (BNF), and pregnenolone-16alpha-carbonitrile (PCN) as well as inhibition by SKF 525-A, metyrapone, alpha-naphthoflavone, and piperonyl butoxide. The principal Phase I pathways are demethylation of the tertiary (DAB) and secondary (MAB) amines and ring hydroxylation. When metabolism was measured with 10,000g supernatant fractions, each pathway responded differently and often independently to the inducers and inhibitors, suggesting that they are catalyzed preferentially by different isozymes of cytochrome P-450. Microsomes from PB-treated animals demethylated and hydroxylated DAB at the same rate as did control microsomes, based on cytochrome P-450 content, whereas microsomes from BNF- or MC-treated animals demethylated more rapidly and hydroxylated more slowly. Microsomes from PB-treated animals demethylated the secondary amine, MAB, more rapidly than the tertiary amine, DAB. Purified cytochrome P-448 from MC-treated animals catalyzed DAB demethylation very readily but hydroxylation very poorly. The turnover number was 10x that seen in microsomes from MC-treated animals. Only one of the four cytochrome P-450 fractions isolated from PB-treated animals had significant activity with DAB and the turnover number of one of these (fraction B) was approx that seen in microsomes. This study supports the concept of selectivity of various isozymes of cytochrome P-450 for the different steps in Phase I metabolism of DAB. Furthermore, it is apparent that the association of certain inhibitors with specific isozymes of cytochrome P-450 is a generalization that requires qualification in terms of the substrate(s) involved. (Author abstract) (49 Refs)

32. EFFECT OF DIAZEPAM ON HEPATOCARCINOGENESIS IN THE RAT.

Hino O, Kitagawa T
Dept. Pathology, Cancer Inst., Tokyo 170, Japan
Toxicol Lett; 11(1/2):155-157 1982

The tumor promoting ability of diazepam on the number and size of enzyme altered islands (EAI) in rat liver was investigated. Ten male Donryu rats were fed a diet containing 500 ppm diazepam (50 mg/kg/day) after initiation with 0.06% 3'-methyl-4-(dimethylamino)-azobenzene. Liver tissue was subsequently examined for ATPase-deficient islands (greater than 50 microns in diameter) at wk 16. Mean EAI values in the treated group were 8.64/square cm, compared to control values of 9.76/square cm. Diazepam induced neither cytomegaly nor reduction of canalicular ATPase activity in the centrolobular hepatocytes. Diazepam is apparently not a tumor promoter like phenobarbital. (14 Refs)

HETEROCYCLIC AMINES

33. MORPHOLOGICAL TRANSFORMATION OF C3H/10T1/2 CL8 CELLS BY PROCARCINOGENS.

Oshiro Y, Balwierz PS
G. D Searle and Co., P.O. Box 5110, Chicago, IL, 60680
Environ Mutagen; 4(2):105-108 1982

Transformation of C3H/10T1/2CL8 cells was attempted using two 3-day periods of exposure to aflatoxin B1 (AFB1), benz(a)anthracene (BAA), 4-nitroquinoline-1-oxide (4NQO), beta-naphthylamine (BNA), and 2-acetylaminofluorene (2AAF) at various concentrations, with replenishment of the medium between the two exposures and during the final 3 days of exposure. Exogenous activation was not used. Transformation was determined according to the criteria of Reznikoff et al. AFB1, BAA, and 4NQO exhibited both Type II and Type III foci sufficiently to indicate detection of morphological transformation. BNA treatment yielded too few Type II foci for a conclusive result, and no Type III foci; 2AAF induced only 1 Type II focus, indicating a negative result. Simply modifying the 10T1/2 transformation method by increasing the exposure from 1 day to 6 days can increase the sensitivity to some procarcinogens that require metabolic activation. (7 Refs)

34. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.

Sivak A, Rudenko L, Teague LG
Arthur D. Little, Inc., Cambridge, MA, 02140
Environ Mutagen; 4(2):143-162 1982

Caffeine effects in culture of rodent and human cells are reviewed, and the effects of caffeine on postreplication repair induced by chemical mutagens in normal human fibroblasts (HS-WP), human xeroderma pigmentosum fibroblasts (SGL), mouse BALB/c-3T3 fibroblasts, Syrian hamster embryo cells (SHE), and Chinese hamster V79 cells are reported. Cells were exposed to UV light (100 ergs/square mm), nitroquinoline-N-oxide (NQO: 2.5 uM), N-acetoxy-N-2-fluorenylacetamide (AFFA: 2.0 uM), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG: 50.0 uM) and then to caffeine (0.05-1.0 milliM). Cytotoxicity was enhanced by addition of caffeine to V79 cells and BALB/c-3T3 cells after exposure to either UV light or AFAA. Postreplication repair of V79 cells was inhibited in cells exposed to UV and AFFA. Postreplication repair was not affected by caffeine at concentrations up to 1.0 milliM in HS-WP, SGL, SHE and mouse BALB/c-3T3 cells after exposure to UV, AFAA, NQO, or MNNG. Repair in BALB/c-3T3 cells exposed to UV or AFAA was also unaffected. The failure of cytoxicity results to agree with repair results for most of these cells indicates that it is incorrect to use cytotoxicity evidence for caffeine to imply that genetic damage has occurred. (49 Refs)

35. MALIGNANT FIBROUS HISTIOCYTOMAS INDUCED BY 4-(HYDROXYAMINO)QUINOLINE 1-OXIDE IN RATS.

Konishi Y, Maruyama H, Mii Y, Miyauchi Y, Yokose Y, Masuhara K
Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara 634, Japan
JNCI; 68(5):859-865 1982

Sc and bone malignant fibrous histiocytomas (MFH) were induced in high incidence in rats by 4-(hydroxyamino)quinoline 1-oxide (4-HAQO). Sc MFH were induced locally by repeated weekly injections of 1 mg 4-HAQO/rat for 4 wk. Between 16 and 48 wk after the final treatment, 13/15 (87%) male noninbred Wistar rats developed tumors. The histologic subtypes of these tumors were as follows: 11 fibrous, 1 myxoid, and 1 giant cell. Bone MFH were induced between 18 and 25 wk by implantation of 4-HAQO (8 mg/rat) into the bone marrow of the tibia in 12/14 (86%) male noninbred Fischer 344 rats. The histologic subtypes of these tumors were as follows: six fibrous, four myxoid, and two giant cell. Morphologically, these MFH appeared similar to human MFH. (Author abstract) (27 Refs)

36. MORPHOLOGIC TRANSFORMATION AND CHROMOSOMAL CHANGES INDUCED BY CHEMICAL CARCINOGENS IN SKIN FIBROBLASTS FROM PATIENTS WITH FAMILIAL ADENOMATOSIS COLI.

Miyaki M, Akamatsu N, Ono T, Tonomura A, Utsunomiya J
Dept. Biochemistry, Tokyo Metropolitan Inst. Medical Science, 3-18-22 Honkomagome, Bunkyoku, Tokyo 113, Japan
JNCI; 68(4):563-571 1982

Skin fibroblasts from patients with familial adenomatosis coli (AC) and normal individuals were treated once with the carcinogen 4-nitroquinoline 1-oxide or N-methyl-N'-nitro-N-nitrosoguanidine and then passaged sequentially. Morphologically altered cells appeared in the cultures of carcinogen-treated AC fibroblasts at passages 6-8 (days 100-140) after treatment with the carcinogens, but carcinogen-treated normal cells and untreated AC and normal cells did not become altered even after cultivation for 25 passages. The cultures containing morphologically altered cells showed characteristics of transformed cells, such as a high frequency of colony formation in soft agarose, increased growth ability, and chromosomal abnormalities. The results suggest that AC patients have increased susceptibility to morphologic transformation and chromosomal changes induced by chemical carcinogens. (Author abstract) (19 Refs)

37. PARENTAL EXPOSURE TO X RAYS AND CHEMICALS INDUCES HERITABLE TUMOURS AND ANOMALIES IN MICE.

Nomura T
Inst. for Cancer Res., First Dept. Surgery, Osaka Univ. Medical Sch., Fukushima-ku, Osaka 553, Japan
Nature; 296(5857):575-577 1982

A summary is presented of the effects of radiation (RT) with x-rays and various chemical in mice studied in multiple generations over a 13-yr period and involving 12,905 live-born mice and 9,645 fetuses from 2,904 parents. There was almost a linear increase in dominant lethals following radiation (RT) of spermatids, spermatozoa, and oocytes. There was no significant increase after treatment of spermatogonia. No increase in dominant lethals was produced by treatment with urethan (U). There was a large and significant increase in anomalies in progeny of parents treated with RT or U; only open eyelid, the predominant non-lethal anomaly, was shown to be transmissible. Both RT and U significantly increased the number of tumors in progeny regardless of which sex was treated. The dose-response data for RT showed a clear increase with dose for treatment of post-meiotic stages in males and less clear results for treatment of spermatogonia. Oocytes at late follicular stages were resistant to 36-108 rad of x-rays but were very sensitive to higher doses. As to site, 87% of induced tumors were in the lung with the remainder in many other sites. To confirm that the induced tumors were heritable, after initial treatment of only the male parent, the F1 progeny of treated parents were mated and their progeny examined. Besides treatment with RT and U, some mice were treated with 4-nitroquinoline 1-oxide. The induced tumors were inherited as if they were dominant mutations with about 40% penetrance. (12 Refs)

38. AN ALKALINE SEPARATION METHOD FOR DETECTION OF SMALL AMOUNT OF DNA DAMAGE.

Sakai K, Okada S

Dept. Radiation Biophysics, Faculty Medicine, Univ. Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

J Radiat Res (Tokyo); 22(4):415-424 1981

The alkaline separation method for detection of DNA damage was made quantitative by calibration with an alkaline sucrose gradient centrifugation, and applied to analysis of DNA damage in cultured mouse leukemic L5178Y cells after x-irradiation. The new method can detect DNA damage, probably scissions and alkali-labile sites, but not sinlge- and double-strand breaks. The method can also detect DNA damage due to ethyl methanesulfonate or 4-nitroquinoline 1-oxide. (14 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
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ANILINES AND EXTENDED ANILINES

1. EFFECT OF 4'-HALOGEN SUBSTITUTION ON THE MUTAGENICITY OF TRANS-4-ACETAMIDOSTILBENE AND TRANS-4-(N-HYDROXYACETAMIDO)STILBENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

Shirota FN, Hanna PE
(c/o Hanna) Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
J Med Chem; 25(5):593-595 1982

The effect of halogen substituents placed at the 4' position of trans-4-acetamidostilbene (1, AAS) to alter the pattern of biotransformation and thus the mutagenicity of these derivatives was evaluated by comparing the mutagenic effects of 1 on Salmonella typhimurium TA-100 with the corresponding 4'-F (2), 4'-Cl (3), and 4'-Br (4) analogues. The mutagenic properties of trans-4-(N-hydroxyacetamido)stilbene (5) and its 4'-F (6), 4'-Cl (7), and 4'-Br (8) derivatives were also evaluated in this system. Both the amides (1-4) and hydroxamic acids (5-8) required the presence of a metabolic activating system prepared from hamster liver in order to produce a mutagenic effect. All of these compounds were mutagenic to TA-100. Their mutagenic po-

HE 20.3173/2:

tencies were markedly influenced by the 4'-halogen substituents, the relative mutagenic potencies of the amides being 2 (4'-F) greater than 1 (4'-H), 3 (4'-Cl) greater than 4 (4'-Br), while the hydroxamic acids followed the order of 1 (4'-H) greater than 2 (4'-F) greater than 3 (4'-Cl), 4 (4'-Br). (Author abstract) (17 Refs)

2. FEEDBACK CONTROL OF CHOLESTEROL BIOSYNTHESIS IN MICE FED THE LIVER CARCINOGENS BENZIDINE AND 2-ACETYLAMINOFLUORENE.

Depass LR, Morris MD
Bushy Run Res. Center, Carnegie-Mellon Univ., 4400 Fifth Ave., Pittsburgh, PA, 15213
Cancer Biochem Biophys; 6(1):47-51 1982

Dietary feedback control (DFC) of hepatic cholesterol synthesis is absent or defective in hepatomas of trout, mouse, rat and man. DFC has also been shown to be defective in rats fed several liver carcinogens including 2-acetylaminofluorene (AAF). These studies have led to the hypothesis that loss of normal DFC is an early and consistent event in the development of liver cancer. To determine whether DFC was defective in 'precancerous' mouse livers, we fed the liver carcinogens AAF (0.05% in chow) and benzidine (0.02% in drinking water) to male BALB/c and C57BL/6 mice for 3 or 6 weeks. We measured sterol synthesis as incorporation of 2-14C-acetate into digitonin-precipitable sterols by liver slices. DFC was tested by adding 2% cholesterol to the diet for 3 days prior to sacrifice. Benzidine (but not AAF) treatment enhanced sterol synthesis in C57BL/6, but not in BALB/c, mice. However DFC was normal in both strains with either carcinogen. The results indicate that defective DFC is not a consistent early finding in animals fed liver carcinogens. Since defective DFC has been a consistent finding in AAF-fed rats, additional research is needed to determine whether the same genetic factors which determine susceptibility to chemically-induced neoplasia are also important in influencing DFC in carcinogen-fed animals. (Author abstract) (32 Refs)

3. CHARACTERIZATION OF MUTAGENIC URINARY AND BILIARY METABOLITES OF THE HUMAN CARCINOGEN, BENZIDINE (BZ), IN THE RAT (MEETING ABSTRACT)

Lynn RK, Rogers RM, Garvie-Gould C, Milam DF, Scott KF, Ilias AM
Department of Pharmacology, Oregon Health Sciences University, Portland, OR, 97201
Fed Proc; 41(3):1574 1982

Bacterial mutagenicity studies of the aromatic amine BZ, suggest that the ultimate carcinogenic moiety is produced via metabolic processes. However, the chemical structure of the ultimate carcinogen(s) is currently unknown. Following iv or oral administrations of 14C-BZ, 75% of the radiolabel was excreted in the feces; approx 20% was found in the urine and 5% remained in the animal 03 days after dosing. In bile exteriorized animals up to 70% of the dose was eliminated in the bile. Urinary and biliary metabolites were separated and quantified by high pressure liquid chromatography, and the individual components characterized by mass spectrometry. N-Acetylation, hydroxylation, and glucuronidation were the major pathways leading to the formation of at least 17 radiolabeled urinary and biliary metabolites. Administration of 35S-sodium sulfate prior to BZ produced at least one BZ metabolite which contained 35S. Several of the urinary and biliary metabolites displayed significant mutagenic activity in the Salmonella typhimurium (TA98)-liver S9-beta glucuronidase assay. (no Refs)

4. METABOLISM OF 2,4-DINITROTOLUENE BY RAT HEPATIC MICROSOMES AND CECAL FLORA.

Dent JG, Schnell SR, Guest D
Chemical Industry Inst. Toxicology, Res. Triangle Park, NC, 27709
Adv Exp Med Biol; 136(partA):431-436 1982

The metabolism of 2,4-dinitrotoluene (2,4-DNT) in hepatic microsomes and in the intestinal flora was investigated. Hepatic microsomes were obtained by preparation of livers from male Fischer 344 rats. Cecal microflora was obtained from male rats. [U-14C] 2,4-DNT was incubated at 100 uM with microsomes in 66 milliMoles tris HCl (pH 7.4) for 1 hr; a NADPH generating system was included. An oxygen scavengering system was included in the incubations with nitrogen. The patterns of metabolites produced by the hepatic microsomes was dependent on the oxygen tensions in the incubations. In contrast to microsomes, cecal microflora did not metabolize 2,4-DNT in an air atmosphere, but the 2,4-DNT was rapidly reduced in anaerobic conditions. Both 2-and 4-nitroso-nitrotoluenes were detected in the cecal flora incubations. Comparison of the metabolism of the DNT by the cecal contents and the hepatic microsomes indicated that the reductive metabolic capacity of the cecal contents on a per g wet wt basis exceeds that of the liver by a factor of 1,000, suggesting that the cecum represents a major site for reductive metabolism of DNT; the 2,4-DNT undergoes reduction at either the 2 or 4 nitro group to a nitroso-nitrotoluene. Reduced metabolites of DNT absorbed from the gut would be substrates for the mixed function oxidase (MFO) enzymes in the liver. Oxidations by the MFO system would lead to highly reactive intermediates in the liver. Thus, the liver and cecal microflora acting in concert may be responsible for the carcinogenic activity of DNT. (7 Refs)

5. MUTAGENICITY OF THREE AROMATIC AMINES IN THE PRESENCE OF FRACTIONS FROM VARIOUS TISSUES.

Fouarge M, Mercier M, Poncelet F
Laboratoire de Toxicologie et Bromatologie, UCL-72.37, Sch. Pharmacy, Avenue E. Mounier 72, B-1200 Brussels, Belgium
Toxicol Lett; 11(3/4):313-320 1982

Salmonella typhimurium strain TA-1538 was used as a test system for mutagenicity studies of 2-aminofluorene (2-AF), 4-aminobiphenyl (4-ABP) and 3,2'-dimethylaminobiphenyl in the presence of post-mitochondrial fractions (liver, kidney, intestine, colon, testicle) of untreated and pretreated rats. The highest mutagenic activity was detected with 2-AF and the lowest with 4-ABP. Activating capacity of liver post-mitochondrial fraction was highest, followed in order by kidney, testicle, intestine, and colon. No relationship was found between the mutagenic activity and the carcinogenicity of the compounds. (20 Refs)

6. METABOLIC ASPECTS OF THE COMUTAGENIC ACTION OF NORHARMAN.

Sugimura T, Nagao M, Wakabayashi K
Natl. Cancer Center Res. Inst., Tsukiji, Chuo-Ku, Tokyo, Japan
Adv Exp Med Biol; 136(partB):1011-1025 1982

Microbial mutagenicity tests were conducted using norharman (beta-carboline) in the Ames Salmonella typhimurium assay with strain TA 98. Comutagenicity of norharman with aniline was demonstrated, and linear dose-response curves were obtained with the aniline metabolites phenylhydroxylamine and nitrosobenzene in the presence of 200 ug norharman. Norharman was comutagenic with o-toluidine, but not with m-

or p-toluidines. It induced mutagenesis in yellow OB dye, but not red dye number 2, which does not yield either aniline or o-toluidine upon hydrolysis. 3-Aminopyridine and 2-amino-3-methyl-pyridine were mutagenic in the presence of norharman, but eight other aminopyridine derivatives were not. Diphenylnitrosamine (DPhN) and diphenylamine (DPhA) were mutagenic in the presence of norharman and S-9 mix, but not without both added components in the incubation medium. Mutagenicity of DPhN seems to be due to DPhA formed metabolically. Other strains of S typhimurium (TA 1538, TA 1978) showed sensitivity to aniline + norharman, and strains TA 100 and TA 1535 were totally unaffected. A mixture of microsomes + supernatant + NADPH yielded more revertants than microsomes alone, microsomes + NADPH, or supernatant + NADPH. (41 Refs)

7. THRESHOLD LEVELS IN TOXICOLOGY: SIGNIFICANCE OF INACTIVATION MECHANISMS.

Greim H, Andrae U, Goggelmann W, Hesse S, Schwarz LR, Summer KH
Dept. Toxicology, Gesellschaft fur Strahlenund Umweltforschung, 8042 Neuherberg, W. Germany
Adv Exp Med Biol; 136(partB):1389-1398 1982

Various in vitro test systems demonstrated that metabolic inactivation of chemicals may prevent toxic effects of reactive intermediates when present in low levels, while inactivation may be overcome at high levels. Reactive oxygen species formed during monooxygenase-mediated metabolism of chemicals can induce DNA repair activity in the human lymphoblastoid cell line NC37 BaEV. Addition of catalase, glutathione, and superoxide dismutase prevents hydroxyurea-induced DNA repair, indicating that H_2O_2 or reactive oxygen species deriving from H_2O_2 are likely to be genotoxic agents. Toxicity studies of chloroprene indicated that no carcinogenic effect could be found, while a slight mutagenic effect was noted with Salmonella typhimurium strains without metabolic activation. This finding is likely due to inactivation by glutathione-conjugations. In the presence of glutathione, chlorodinitrobenzene was not mutagenic in Salmonella typhimurium. However, at concentrations exceeding those of glutathione, it was increasingly mutagenic. Irreversible binding of naphthalene was increased by suppression of glucuronidation and sulfation in isolated hepatocytes. These findings demonstrate that two threshold doses can be observed: a no-effect level and a level at which the toxic effects disproportionally increase when high concentrations of a chemical are present and inactivation can be overcome. The relevance of extremely high doses often used in animal experiments for studying embryo toxicity or in other chronic toxicity studies is questioned. (25 Refs)

8. STIMULATION OF DRUG AND CARCINOGEN METABOLISM BY PROLONGED ORAL TOBACCO CONSUMPTION.

Kaur S, Ali B
(c/o Ali) Jawahar Lal Nehru Lab. Molecular Biology, King George's Medical Coll., Lucknow-226003, India
Biochem Pharmacol; 31(8):1595-1597 1982

Oral administration of tobacco to rats for 21 days caused remarkable stimulation of the metabolism of phenacetin, aniline and benzo[a]pyrene, a carcinogen, by hepatic microsomal mixed function oxidases (MFO). Such treatment for 6 days resulted in a small increase in the activities of phenacetin O-dealkylase and aromatic hydrocarbon hydroxylase (AHH) without affecting aniline hydroxylase activity. Nicotine given orally was found to be a relatively weak inducer of phenacetin O-dealkylase and aniline hydroxylase, and elicited a maximum increase in their activities within 6 days which remained unchanged even after 21 days of continuous administration. However, these two enzyme systems were not affected following only one or two doses of tobacco and nicotine. Both tobacco and nicotine inhibited these biotransformations in vitro. (Author abstract) (15 Refs)

9. ADP-RIBOSYLTRANSFERASE ACTIVITY IN CULTURED HEPATOCYTES. INTERACTIONS WITH DNA REPAIR.

Althaus FR, Lawrence SD, Sattler GL, Pitot HC
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
J Biol Chem; 257(10):5528-5535 1982

A rapid increase in ADP-ribosyltransferase activity was observed when freshly isolated hepatocytes derived from adult rats were established in primary monolayer culture. (ADP-ribose)n-degrading activity remained constant over a period of 48 hr of culture. Inhibition of ADP-ribosyltransferase activity with pyridine derivatives, 3-aminobenzamide, theophylline, or thymidine, was accompanied by an enhanced DNA repair synthesis in response to the direct-acting carcinogen, methyl methanesulfonate, or UV irradiation. Three aminobenzamides differing only in the position of the amino group exhibited the same structure-activity relationship in regard to their action on DNA repair synthesis and ADP-ribosyltransferase. Spermine treatment of hepatocytes apparently had an inverse effect on both these cellular functions. The removal of DNA strand breaks following methyl methanesulfonate treatment was accelerated by inhibitors of ADP-ribosyltransferase. The results suggest that ADP-ribosylation interacts with late stages in the process of DNA repair. This interaction apparently is dependent on the nature of damage imposed on chromatin since repair synthesis in response to a number of carcinogens is unaffected by inhibitors of ADP-ribosyltransferase. (Author abstract) (52 Refs)

10. COVALENT CROSS-LINKING OF A PHOTOACTIVE DERIVATIVE OF CALCITONIN TO HUMAN BREAST CANCER CELL RECEPTORS.

Moseley JM, Findlay DM, Martin TJ, Gorman JJ
Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria, 3077, Australia
J Biol Chem; 257(10):5846-5851 1982

A photoaffinity derivative of salmon calcitonin has been produced by transglutaminase-mediated incorporation of N-(beta-aminoethyl)-4-azido-2-nitroaniline into the hormone. The derivative, purified by high pressure liquid chromatography, retained the abilities to bind to cultured T47D breast cancer cells and to stimulate adenylate cyclase in these cells. In both these respects it was equipotent with synthetic salmon calcitonin. Photolysis of the 125I-labeled photoactive salmon calcitonin derivative bound to T47D cells was accompanied by specific labeling to only one component ($M_r = 85{,}000$) as assessed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Labeling was observed only upon photolysis and was inhibited by unlabeled synthetic salmon calcitonin but not by the inactive calcitonin analogue, 8-glycine human calcitonin. Reduction did not alter the apparent mol wt of the calcitonin receptor complex. No macromolecular forms of calcitonin were produced by photolysis in the absence of T47D cells. (Author abstract) (29 Refs)

11. THE TERATOGENICITY OF THE AMINOPHENOLS (AP) IN SYRIAN GOLDEN HAMSTER (SGH) (MEETING ABSTRACT)

Rutkowski JV, Ferm VH
Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH
Toxicologist; 2(1):69 1982

It is known that p-AP (p-aminophenol) has been recently demonstrated to be a metabolic product of the analgesic-antipyretic agent, acetaminophen. p-AP is a cytotoxic chemical due to its action as a metabolic inhibitor. This study was undertaken to evaluate the teratogenic potential of p-AP and the other isomeric forms, m-AP and o-AP. Timed pregnant SGH (LKV strain) were used. Day 1 of gestation is that day following the evening of breeding. On the morning of day 8 of gestation the SGH received an ip dose of 100-200 mg/kg of p-AP, o-AP, or m-AP. The dams were sacrificed on day 13 of gestation. p-AP and o-AP produced a significant teratogenic response. A dose-effect phenomenon was evident by a rise in the frequency of litters with one or more malformed fetuses. The total number of fetuses with one or more malformations also increased with dose, as did the resorption response. Frequently observed malformations were exencephaly, encephalocoele, eye defects, rib fusion, tail defects, spina bifida, limb defects, and umbilical hernia. Other rare malformations were also noted. (no Refs)

12. DINITROTOLUENE PROMOTION OF DIETHYLNITROSAMINE (DEN) INITIATED HEPATOCYTES IN VIVO (MEETING ABSTRACT)

Leonard TB, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 2(1):100 1982

Technical grade DNT (dinitrotoluene) (tDNT) is a potent hepatocarcinogen when fed to F-344 male rats for one year (100% incidence of hepatocellular carcinomas). The present studies were designed to ascertain whether tDNT had promoting activity and to investigate the mechanism of tDNT promotion. Male F-344 rats were treated with a single dose of DEN (150 mg/kg), permitted to recover for 2 wk, and then fed tDNT in the diet for 3 wk. Promotion activity was quantitated by determining the incidence of histochemically identifiable hepatic gamma-glutamyl transpeptidase positive (GGT+) foci. Feeding 14 mg/kg/day and 35 mg/kg/day of tDNT caused a dose-dependent increase in GGT+ foci relative to initiation control and promotion control values. To investigate the mechanism of tDNT promotion, the effectiveness of tDNT (35 mg/kg/day) as a replacement for 2-acetyl-aminofluorene (2-AAF) in a hepatic 'growth selection' protocol and its ability to alter DNA synthesis in hepatocytes following partial hepatectomy (PH) were determined. tDNT was active in the growth selection protocol but not as effective as 2-AAF. When tDNT was fed (35 mg/kg/day) for 2 wk prior to PH, it had no effect on the kinetics of DNA synthesis following PH. (no Refs)

13. IN VITRO CARCINOGENESIS IN CANINE BLADDER (MEETING ABSTRACT)

Klaunig JE, Constantini MG, Barut BA, Goldblatt PJ
Department of Pathology, Medical College of Ohio, Toledo, OH
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

As part of our overall investigation of mechanisms of bladder carcinogenesis, we have developed methods for establishing primary and secondary cultures of canine bladder urothelial cells. Urinary bladders from adult dogs of mixed breed were removed immediately after exanguination. Four pieces of bladder (0.5 x 0.5 cm) were placed urothelium side up per 60-mm culture dish. Two milliliters of Ham's 151 culture medium were added per dish, and dishes were maintained at 36.5 C in a humidified CO2 incubator. Epithelial cells were seen extending from the explants 2 to 3 days after culture initiation. Within 2 to 3 weeks cells were almost confluent on the culture dish. The inclusion of fetal bovine serum in the medium resulted in the overgrowth of epithelial cultures by fibroblasts. The calcium concentration in the medium had a significant influence on differentiation and growth of primary urothelial cells. A concentration of 1 x 10(-4) M calcium appeared optimal for cell growth and prevention of differentiation. Secondary cultures were initiated by trypsinization of primary cultures. Fetal bovine serum was required in the medium for secondary culture cell growth. DNA repair (measured by inductor of unscheduled DNA synthesis (UDS) was evident in explants, primary, and secondary cultures following exposure to methylnitrosourea, aflatoxin B1, 4-aminobiphenyl, and benzo(a)pyrene. UDS in each compound displayed a linear dose response. Radiolabeled benzo(a)pyrene was metabolized and covalently bound to DNA in bladder explants primary and secondary cultures. (no Refs)

FLUORENAMINES: IN VIVO

14. INDUCTION OF HYPERPLASTIC LIVER NODULES IN HEPATECTOMIZED RATS TREATED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, BENZO[A]PYRENE OR PHENOBARBITAL BEFORE OR AFTER EXPOSURE TO N-2-FLUORENYLACETAMIDE.

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Gann; 73(2):264-269 1982

The effects of pre- and post-administration of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), benzo[a]pyrene (B[a]P), and phenobarbital (PB) on the induction of hyperplastic liver nodules by N-2-fluorenylacetamide (2-FAA) were studied in F344 rats. Rats were given 3'-Me-DAB (0.06% in the diet), B[a]P (80 mg/kg b wt x 7, intragastrically) or PB (0.05% in the diet) for 6 wk before (experimental series I) or after (experimental series II) diet containing 0.02% 2-FAA for 2 wk, and killed in wk 10 of the experiment. The number and total area of hyperplastic nodules per unit area of liver were greatest in rats treated with 3'-Me-DAB in both experimental series. B[a]P significantly increased the induction of hyperplastic nodules in experimental series I and PB significantly increased it in experimental series II. Partial hepatectomy performed during administration of test chemicals enhanced the induction of hyperplastic nodules, especially in experimental series I, and an oral dose of carbon tetrachloride during 2-FAA feeding enhanced it in both experimental series. In the present system, initiating activity of both the hepato- and the non-hepatocarcinogen was detected, and promoting activity of both the hepatocarcinogen and the hepatopromoter was demonstrated. (Author abstract) (23 Refs)

15. METABOLISM AND NUCLEIC ACID BINDING OF 7-FLUORO-2-ACETAMIDOFLUORENE IN RATS: OXIDATIVE DEFLUORINATION AND APPARENT DISSOCIATION FROM HEPATOCARCINOGENESIS OF 8-(N-ARYLAMIDE)GUANINE ADDUCTS ON DNA.

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Chem Biol Interact; 40(1):27-43 1982

The significance in hepatocarcinogenesis of various arylamine/amide adducts with nucleic acid was investigated. Female Fischer and Sprague-Dawley rats are comparably sensitive to hepatocarcinogenesis by 2-acetamidofluorene (AAF), while male rats are more sensitive. 7-Fluoro-2-acetamidofluorene is more carcinogenic in Sprague-Dawley rats than is AAF, and strikingly so toward the liver of female rats. Binding of both compounds to liver nucleic acids was determined for Fischer rats at 1 and 3 days after a single injection of carcinogen, and in female Sprague-Dawley rats from 1 to 28 days after a single injection. No 8-(N-2-fluorenylacetamido)guanine adduct or the 7-fluoro derivative could be found in RNA or DNA of female Sprague-Dawley rats treated with AAF These adducts were present in comparable amounts in both male and female Fischer rats. The binding of 7-fluoro-AAF derivatives was higher than that of AAF derivatives in female Sprague-Dawley rats. Feeding of either AAF or 7-fluoro-AAF to Sprague-Dawley rats for 4 wk before a single injection of [3H]7-fluoro-AAF resulted in reduction of the 8-(N-2-(7-fluoro)fluorenyl-acetamido)guanine adduct in males to undetectable levels in DNA and to 10% of control level in RNA. Non-acetylated adducts were increased in males, but decreased in females by AAF prefeeding; 7-fluoro-AAF prefeeding resulted in little change in adduct formation in females and in a major increase in non-acetylated adducts in males. AAF adducts disappeared from DNA more rapidly than did 7-fluoro-AAF adducts. Assay of the urinary metabolites from the animals in the prefeeding experiment showed that all compounds fed increased the proportion of N-hydroxy-7-fluoro-AAF among the metabolites. Defluorination of 7-fluoro-AAF to 7-hydroxy-AAF was also demonstrated and the ratio of 7-hydroxy-AAF to 5-hydroxy-7-fluoro-AAF was comparable to that observed for 7-hydroxy-AAF/5-hydroxy-AAF and AAF itself, suggesting that fluoro substitution does not increase activity by preventing detoxication. (28 Refs)

16. EFFECTS OF ALPHA-NAPHTHYLISOTHIOCYANATE, LITHOCHOLIC ACID AND SELECTED HEPATOCARCINOGENS ON EPOXIDE HYDROLASE, DT-DIAPHORASE AND SERUM INDICATORS OF CHOLESTASIS (MEETING ABSTRACT)

Thompson MB, Dent JG, Graichen ME, Neptun DA, Scortichini BH, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709

Toxicologist; 2(1):101 1982

The classic cholestatic agent alpha-naphthylisothiocyanate (ANIT) elevates the hepatic preneoplastic marker epoxide hydrolase (EH). Abilities of 3 hepatocarcinogens and 2 cholestatic agents to produce cholestasis and enhance hepatic EH activity were compared. Hepatocarcinogens 2-acetylaminofluorene (AAF) at 100 ppm or 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) at 600 ppm in the diets or diethylnitrosamine (DEN) at 40 ppm in the drinking water were given to male, Fischer-344 rats (200-270 g). The cholestatic agents ANIT at 1000 ppm or lithocholic acid (LA) at 10,000 ppm in the diets were fed to comparable groups. Concentrations of total bile acids (BA), total cholesterol (CH) and total bilirubin (BIL) and the activity of gamma-glutamyltranspeptidase (GGT) were measured in serum at 2, 4 and 6 weeks. Activities of hepatic microsomal epoxide hydrolase (EH) and cytosolic DT-diaphorase (DTD) were determined. Serum BA concentrations were increased by all treatments. ANIT treatments produced the greatest increases. AAF an 3'-MeDAB caused intermediate increases and DEN and LA the smallest. CH and BIL concentrations and activities of GGT and DTD were only increased by treatment with ANIT. EH was increased by all treatments except LA. At 2 and 6 weeks animals exposed to AAF, DEN and 3'-MeDAB had a direct correlation between serum BA and EH activities. (no Refs)

17. QUANTITATIVE ASSESSMENT OF CARCINOGEN-MODIFIED DNA IN SPECIFIC LIVER CELL POPULATIONS FOLLOWING A SINGLE DOSE N-2-ACETYLAMINOFLUORENE (AAF) OR ITS N-HYDROXY DERIVATIVE (N-OH-AAF) (MEETING ABSTRACT)

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Toxicologist; 2(1):103 1982

AAF-induced hepatocarcinogenesis appears to be targeted to parenchymal cells (PC). Our objective was to determine whether or not there is preferential binding of carcinogen (C) residues to the DNA of these target cells and, if so, the possible basis for the selectivity. AAF and its N-hydroxy derivative (N-hydroxyl-N-2-acetylaminofluorene), the first product in the metabolic activation of AAF, were employed for these studies. Male Sprague-Dawley rats weighing 200-250 g were injected, ip, with (ring-3H)AAF or (ring3H)-N-OH-AAF. Animals were sacrificed at either the time of peak binding of C to DNA, 2 hr or 18 post-injection, when N-OH-AAF or AAF, respectively, were used, and at 3 days after maximum binding. PC and nonparenchymal (NPC) cells were isolated by centrifugal elutriation. Following AAF administration, the u moles of adducts formed/mg DNA of PC was 2.7 times that of the NPC. When N-OH-AAF was employed, equal amounts of adducts were found associated with DNA of PC and NPC. By 3 days after the period of maximum DNA binding 50-59% of the adducts initially present remained in the DNA of both cell types following administration of either AAF or N-OH-AAF. These results suggest that AAF preferentially damages DNA of PC due to an increased capacity of these cells to carry out the N-hydroxylation of AAF. (no Refs)

18. TESTICULAR MESOTHELIOMAS IN RATS EXPOSED TO N-2-FLUORENYLACETAMIDE (FAA) (MEETING ABSTRACT)

Cabral JR, Neal GE
International Agency for Research on Cancer, Lyon, France

Toxicologist; 2(1):105 1982

The incidence of testicular mesotheliomas due to the carcinogen FAA was studied in four-week-old male Fischer 344 rats. The experimental animals were fed the carcinogen diet (0.06% FAA) during 3 weeks and then the control diet for 1 week. This schedule was carried out for 3 complete cycles (12 weeks). A smaller group of rats was treated for 1 complete cycle only (4 weeks) of FAA. One group of untreated controls was also available. The surviving rats were sacrificed at 59 weeks of age. The administration of FAA for 3 complete cycles resulted in a high incidence of liver, testis and Zymbal gland tumors. The testicular tumors were mesotheliomas and occurred in 9/25 rats. No such tumors were observed in animals treated for 1 cycle only or in untreated controls. Macroscopically, these tumors appeared as flat, nodular or papillary, greyish or pinkish growths on the surface of the testis and/or epididymis. Microscopically, the tumors were seen to arise from the surface of the peritesticular mesothelium. The first testicular mesothelioma was observed 30 weeks after end of treatment. No metastases from these tumors were found. The high incidence of testicular mesotheliomas, a rare type of tumor in this and other rat strains, suggests an association with treatment. (no Refs)

19. ISOLATION AND TRANSPLANTATION OF PRECURSORS IN HEPATOCARCINOGENESIS (MEETING ABSTRACT)

Miller SB, Pretlow TP, Pretlow TG
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71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

The role of cells frequently termed putative preneoplastic cells in hepatocarcinogenesis is still unclear. Two types of cells widely regarded as possible precursors of hepatomas are the 'enzyme-altered hepatocyte' and the 'oval cell'. Both of these cells have histochemically demonstrable gamma-glutamyl transpeptidase (GGT). We have attempted to isolate each of these cell types free of the other to test their biologic potentials. Half a billion liver cells were purified by velocity sedimentation in the Dupont-Sorvall TZ-28 reorienting zonal rotor. When purified preparations of 98.8 per cent hepatocytes were injected into the mesenteric veins of syngeneic rats fed a diet with 0.02 per cent acetylaminofluorene and subjected to partial hepatectomy, all rats developed foci of cells with GGT in their livers in 10 days. Type II cells, small cells with intense GGT, were purified in an isokinetic gradient followed by free-flow electrophoresis. Preparations with 37.2 per cent type II cells and only 1.6 per cent hepatocytes were injected into syngeneic hosts prepared as described above. Recipients of type II cells also developed hepatic foci with GGT within 10 days. Both enzyme-altered hepatocytes and type II cells make up part of what previously has been referred to as 'liver colony-forming units'. (no Refs)

FLUORENAMINES: IN VITRO

20. IN VITRO INHIBITION OF LIVER MICROSOMAL ARYLAMIDE N-HYDROXYLASE.

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Adv Exp Med Biol; 136(partB):1203-1211 1982

In vitro effects of various chemicals on the liver microsomal (LM) N-hydroxylase (NH) activity from control or 3-methylcholanthrene (3-MC) pretreated rat, hamster, and mouse are discussed. Pretreatment with 3-MC induces NH activity in all three species: 30-fold in rat, 12-fold in hamster, and 5-fold in mouse. Submicromolar concentrations of 3-MC, 7,8-benzoflavone, and benzo(a)pyrene inhibit LM 2-acetylaminofluorene (2-AAF) NH from both control and 3-MC pretreated hamster, rat, and mouse. Inhibitor of microsomal deacetylase, paraoxon, also inhibited NH of rat, hamster, and mouse microsomes. NH activity decreased progressively with increasing concentrations. At 5 uM of paraoxon, the enzyme activity (at 0.25 uM concentration of 2-AAF) was inhibited by 20%, at 50 uM by 70%, and at 200 uM by 85%. Strong inhibition of 2-AAF N-hydroxylation was observed with 1-acetylaminofluorene and 3-acetylaminofluorene, whereas 4-acetylaminofluorene had no such effect. The 1-and 3-isomers appeared thus to bind the enzyme. Added in vitro to the incubation medium (at 50 uM) norharman and harman inhibited the liver microsomal N-hydroxylation of 2-AAF (0.25 uM). Liver microsomes from both control and 3-MC treated rat, hamster, and mouse were all sensitive to the inhibition which varied from 60% for rat to 80% for hamster and mouse. The effect of harman was dose-dependent. Results indicate that the mouse appeared to be most effective in N-hydroxylating 2-AAF. (16 Refs)

21. OPTIMUM S9 CONCENTRATIONS IN BACTERIAL MUTAGENICITY ASSAYS.

Forster R, Green MH, Priestley A
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Adv Exp Med Biol; 136(partB):1263-1269 1982

Activation of 2-acetylaminofluorene (AAF) in two assay systems using bacterial mutagenesis is discussed. A modified incubation mixture was prepared, containing soft agar, which was dispensed to either Ames test (AT) plates or fluctuation test (FT) replicate tubes. Results indicate that the soft agar and temperature change cause some loss of activity and have a slight effect on the S9 optimum compared with a conventional FT. The S9 optimum of the modified FT could be compared with the response in a conventional FT. The S9 optimum is altered in the modified test and resembles a characteristic AT response. The same result was obtained when purified microsomes were used for activation instead of S9-mix indicating that the diffusion of cytosolic constituents of S9 fraction is not responsible for the difference. The concentrations of NADPH and NADPH generating system do not influence the S9 optimum. The diffusing factor was investigated by the addition of a number of agents to FT incubate. The presence of corn oil increased and broadened the S9 optimum suggesting that the agent is lipophilic. The addition of DNA (57 ug/ml), protein (2.5 mg/ml bovine serum albumin), or glutathione (2.5 mg/ml), and uridine diphosphate glucuronic acid (250 ug/ml) did not affect the S9 optimum. The effects of two ring hydroxylated AAF metabolites on the activation of AAF were examined in an AT. While the 1-OH metabolite had a slight inhibitory effect on AAF activation, the 7-hydroxy metabolite had a stimulatory effect on AAF activation. Results suggest that feedback effects of relatively unreactive metabolite of AAF may offer a mechanism for the apparent diffusible inhibition of microsomal activation but if so the action of the metabolite must be complex. (4 Refs)

22. MICROSOMAL METABOLISM OF 2-ACETYLAMINOFLUORENE, ROLE IN MUTAGENICITY AND CARCINOGENICITY.

Roberfroid M, Razzouk C, Agazzi-Leonard E, Batardy-Gregoire M, Poncelet F, Mercier M
Lab. Biotoxicology, Universite Catholique de Louvain, UCL 73.69, B-1200 Brussels, Belgium
Adv Exp Med Biol; 136(partB):921-929 1982

Biochemical properties of microsomal enzymes catalyzing endoplasmic reticulum-mediated metabolism of 2-acetylaminofluorene (2AAF), including reactions of primary activation and detoxification, were studied as means of elucidating the mechanism of biological effects of 2AAF. Correlation of kinetic parameters of liver microsomal N-hydroxylase with carcinogenic effects showed that the rat is the most susceptible species, but exhibited the lowest activity, whereas the mouse is the least susceptible species, but it has the highest enzyme activity. The rat liver microsomal N-hydroxylase showed the highest affinity for 2AAF, whereas the mouse liver enzyme had the lowest affinity. Mutagenicity of the animal microsomal preparations correlated well with their enzyme activities ranking in the order hamster = mouse much greater than rat in terms of the Ames test with 2AAF as a promutagen. Kinetic parameter studies with rat liver microsomal N-hydroxylase showed that 2AAF and 2-aminofluorene modified the enzyme, but other aminofluorene isomers did not. Feeding the rat with 2AAF and 3-methylcholanthrene (3MC) resulted in a competitive inhibition in the endoplasmic reticulum that reduced N-hydroxylating capacity. Similar behavior of 3MC in the hamster results in the initiation of cancer because the hamster liver N-hydroxylase activity is far higher than that of the rat liver enzyme so that there is production of sufficient N-hydroxy-metabolite to initiate cancer. (18 Refs)

23. METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE.

Thorgeirsson SS, Wirth PJ, Staiano N, Smith CL
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Adv Exp Med Biol; 136(partB):897-919 1982

Metabolic activation of 2-acetylaminofluorene (2AAF) by rat N-hydroxy-2-acetylaminofluorene (N-OH-AAF) N-O-acyltransferase and N-OH-AAF sulfotransferase and mutagenicity of 2AAF in the Ames mutagenicity test are described. Partially purified rat liver N-O acyltransferase markedly increased mutagenicity of N-OH-AAF in the Salmonella test system. With sulfotransferase, the capacity to activate mutagenesis of N-OH-AAF in this assay decreased with each step of purification. Incubation of partially purified N-O acyltransferase with N-OH-AAF and yeast transfer tRNA results in an approx 15-fold increase in the extent of covalent binding of (9-14C) N-OH-AAF to the tRNA. Similar experiments with partially purified sulfotransferase gave no catalysis of covalent binding beyond that observed with the 105,000 g supernatant fraction, unless 3'-phosphoadenosine-5'-phosphosulfate was added; then a 60-fold increase in covalent binding of N-OH-AAF to tRNA was observed. Both ascorbate and NADPH markedly inhibited the covalent binding. The most recent tests system utilizes isolated hepatocytes together with Salmonella tester strains to measure mutagenicity of 2AAF, 2-aminofluorene, and N-OH-AAF. (36 Refs)

24. RADIOIMMUNOASSAY FOR 2-ACETYLAMINOFLUORENE-DNA ADDUCTS.

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In Vitro Pathogenesis Section, NCI, NIH, Bethesda, MD, 20205
Methods Enzymol; 84:607-618 1982

Methods for the synthesis of N-(8)-guanosinylacetylaminofluorene, its coupling to bovine serum albumin, and immunization of rabbits are described. Procedures for the establishment of a radioimmunoassay for both N-(8)-deoxyguanosinylacetylaminofluorene and N-(8)-deoxyguanosinylaminofluorene are outlined, and examples of the application of this assay to quantify DNA-bound carcinogen in hydrolyzed DNA from different types of cultured cells exposed to N-acetoxy-2-acetylaminofluorene are presented. The quantification of acetylated and deacetylated C-8 adducts depends on specificity of the particular antiserum. (20 Refs)

25. IN VITRO INHIBITION OF DNA METHYLASE (DMASE) BY DIRECT CARCINOGENS AND THE PROTECTIVE ABILITY OF THIOL REDUCING AGENTS (MEETING ABSTRACT)

Chan JY, Ruchirawat M, Lapeyre JN, Becker FF
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Fed Proc, 41(3):685 1982

The role of DNA methylation during carcinogenesis is unknown although DNA from carcinogen-treated rat liver is hypomethylated. To determine if carcinogens directly affect DMase, the direct-acting carcinogens acetoxyacetylaminofluorene (AcAAF) and methylnitrosourea (MNU) were tested in vitro on DMase activity from rat liver. Fifty percent inhibition of DMase activity was achieved with 4.3 mM AcAAF and 47 mM MNU. The sensitivity of DMase towards direct carcinogens was similar to that for DNA polymerase-alpha, while DNA polymerase-beta, the putative repair enzyme, was highly resistant to carcinogen damage. When various thiol reducing agents were tested for their ability to protect DMase from carcinogen damage, differential protective ability was observed. Dithiothreitol, beta-mercaptoethanol and reduced glutathione were effective in protecting DMase from AcAAF damage while the effects of cysteine and ergothioneine were small. At 10 mM of these agents, the percent of DMase activity recovered after interaction with 6.7 mM of AcAAF was 94,86,78,34 and 12, respectively. These effects may have some bearing on the DNA hypomethylation observed in vivo, suggesting that the carcinogens tested may achieve their inhibitory effect by affecting crucial thiol(s). These data also suggest that various intracellular thiols may play an important role in protecting DNA modifying enzymes from carcinogen damage. (no Refs)

26. FURTHER STUDIES ON THE CO-TRANSFORMATION OF DISTANT MARKERS FOLLOWING THE EXPOSURE OF DNA TO CARCINOGENS INCLUDING CARCINOGENIC METALS (MEETING ABSTRACT)

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Fed Proc; 41(3):685 1982

Exposure of Bacillus subtilis transforming DNA to chemical carcinogens produced a decrease in transforming activity of such DNA and a decrease in co-transformation of linked markers (tyr-trp). Under carefully controlled conditions an increase in co-transformation of distant (unlinked) markers (tyr-leu and trp-leu) was detected, indicating the formation of DNA-DNA complexes capable of penetrating into the interiors of the recipient cells. However, based on our studies of N-acetoxy-2-acetylaminofluorene - treated DNA, up to 80% of these complexes were eventually 'repaired', restoring the original chromosomal locations of these unlinked markers. Occasionally, the artificially linked pieces of DNA were inserted into adjacent loci in the recipients cell's chromosome. In separate studies, effects of various salts of chromium on the transforming DNA were investigated. An increased co-transformation of the unlinked markers was observed with Cr VI but not with Cr II or Cr III. The former, but not the latter are believed to produce tumors in humans. Thus, these observations support our earlier suggestion that only those mutational events which produce macromolecular complexes may be responsible for the malignant transformation in vivo. (no Refs)

27. DIETARY SELENIUM, HEPATIC ARYLHYDROCARBON HYDROXYLASE AND MUTAGENIC ACTIVATION OF BENZO(A)PYRENE, 2-AMINOANTHRACENE AND 2-AMINOFLUORENE.

Gairola C, Chow CK
Tobacco and Health Res. Inst., Lexington, KY, 40506
Toxicol Lett; 11(3/4):281-287 1982

Young (5-6 wk old) and adult (66 wk old) male Sprague Dawley rats were maintained on a low selenium (Se) basal diet with or without 1 or 2 ppm Se supplement for 5 or 20 wk. Five days prior to sacrifice, the animals were injected ip with Aroclor to determine aryl hydrocarbon hydroxylase (AHH) inducibility. Using the Ames Salmonella/microsome mutagenicity assay, the activation potential of the liver postmitochondrial supernatant was determined using benzo(a)pyrene (BP), 2-amino-fluorene (2AF) and 2-acetyl aminofluorene (2AAF) as potential mutagens. Low dietary Se caused a reduced AHH level in young control rats but dietary Se had no effect on AHH inducibility in both dietary groups. Since Se is a cofactor for glutathione peroxidase (GSH-P), the levels of GSH-P were decreased more in young rats by low dietary Se. Dietary Se did not appreciably affect the activation of BP, while low dietary Se affected the mutagenic activation of 2AF and 2AAF. (24 Refs)

28. REACTIVE INTERMEDIATES OF 2-ACETYLAMINOFLUORENE METABOLISM IN VITRO COVALENTLY LABEL SPECIFIC RAT LIVER MICROSOMAL PROTEINS.

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Biological Lab., Univ. Kent, Canterbury CT2 7NJ, England
Adv Exp Med Biol; 136(partB):1183-1191 1982

Labeling of individual microsomal proteins during the metabolism of 2-acetylaminofluorene (AAF) in vitro was studied using electrophoretic techniques. After incubation of rat liver microsomes with (9-14C)AAF in the presence of NADPH, 3-5% of the added label was tightly bound to the membrane. Solubilization of this label by pronase and trypsin treatment indicated that the labeled derivative is covalently bound to microsomal protein. The binding increased linearly with time and was totally dependent on the presence of NADPH. With microsomes from 3-methylcholanthrene (MCA)-induced rats, binding was increased eight-fold compared to controls, but the increase was only two-fold with microsomes from phenobarbital (PB)-induced rats. These findings suggested that the reactive intermediate is generated by a cytochrome P-448-dependent reaction. Binding to microsomes was slightly enhanced by the presence of cytosolic proteins. The incorporation of label was mainly in a few protein bands. Mol wt of these bands were close to those of cytochrome P-450, cytochrome b5, and their reductases. Although the extent of labeling of these proteins increased with time of reaction, the pattern of labeling was not altered. With microsomes from MCA-induced rats, the pattern was similar to that with control microsomes, but with microsomes from PB-induced rats only a single band was labeled significantly corresponding to a PB-induced cytochrome P-450 apoprotein. With microsomes from rats pretreated with AAF, the pattern of labeling was similar to that with controls and MCA-induced rats. Extensive labeling of a band specifically induced by AAF pretreatment was observed. The band was identified as epoxide hydratase. (no Refs)

29. METABOLISM AND MUTAGENIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY HUMAN LIVER AND LUNG.

Boobis AR, Brodie MJ, McManus ME, Staiano N, Thorgeirsson SS, Davies DS
Dept. Clinical Pharmacology, Royal Postgraduate Medical Sch., London, England
Adv Exp Med Biol; 136(partB):1193-1201 1982

Ability of microsomal fractions of human liver to metabolize 2-acetylaminofluorene (2-AAF) and the capacity of subcellular fractions of human liver and lung to convert 2-AAF and N-hydroxy-2-acetylaminofluorene (N-OHAAF) to mutagens were investigated. Microsomal fractions of human liver were relatively active in metabolizing 2-AAF, total oxidative metabolism being greater than that of male Sprague-Dawley rats. Rank order of activities with human liver was 7-hydroxylation greater than 3-hydroxylation greater than 9-hydroxylation greater than 5-hydroxylation. Thus, man is much more active at N- and 3-hydroxylation of 2-AAF than either rat or Rhesus monkey. In biopsies with preserved hepatic architecture, cigarette smoking was associated with significant increases in arylhydrocarbon hydroxylase (AHH) and 1-acetylaminofluorene 3-hydroxylase (2-AAF-3H) activities but not with any significant change in the other 2-AAF hydroxylases or in total cytochrome P-450 content. The correlation between 2-AAF-3H and AHH was significant (0.778) but both enzyme activities were increased in cigarette smokers. When the correlation coefficient was calculated for the non-smokers it was 0.532. The correlation between 2-acetylaminofluorene 7-hydroxylase and AHH was relatively poor (0.668) but only AHH activity was increased in cigarette smokers. No significant correlation between 2-acetylaminofluorene N-hydroxylase and AHH activities (0.554) could be seen. In non-smokers the correlation coefficient was only 0.452. Human liver microsomal fraction activated both 2-AAF and N-OHAAF into a mutagen, whereas human lung post-mitochondrial fraction activated only N-OHAAF into a mutagen. Considerable inter-individual variation in the ability of human tissue samples to activate 2-AAF into a mutagen was observed. The ability of microsomal fractions of human liver to activate 2-AAF to a mutagen did not correlate with N-hydroxylase activity nor with any other enzyme activity measured. Mutagenic activation of 2-AAF and N-OHAAF was unaffected by cigarette smoking. (16 Refs)

30. FORCE FIELD CONFORMATIONAL ANALYSIS OF AMINOFLUORENE AND ACETYLAMINOFLUORENE SUBSTITUTED DEOXYGUANOSINE.

Lipkowitz KB, Chevalier T, Widdifield M, Beland FA
Dept. Chemistry, Indiana Univ.-Purdue Univ. Indianapolis, Indianapolis, IN, 46206
Chem Biol Interact; 40(1):57-76 1982

The hepatocarcinogen N-hydroxy-2-acetylaminofluorene forms two C8-substituted deoxyguanosine adducts in vivo. The conformation of these adducts, as well as 2'-deoxyguanosine and 8-amino-2'-deoxyguanosine has been studied with Allinger's force field. Using the glycoside rotation as a reaction coordinate, multidimensional potential energy surfaces were determined by relaxing all internal degrees of freedom. The calculations indicate the 2'-deoxyguanosine should exist as a mixture of syn and anti forms, that the syn form is slightly favored for 8-amino-2'-deoxyguanosine, that N-(deoxyguanosin-8-yl)-2-acetylaminofluorene (dG-C8-AAF) will only be found in the syn conformation and that, although the syn form is also more stable for N-(deoxyguanosin-8-yl)-2-aminofluorene (dG-C8-AF), it will have a substantially greater proportion of the anti-conformer than is found with dG-C8-AAF. The results of the force field calculations are discussed in relation to the effects these adducts may have on DNA structure. (Author abstract) (55 Refs)

31. QUANTITATIVE ANALYSIS OF THE RING-HYDROXYLATED METABOLITES OF 2-FLUORENYLACETAMIDE BY GAS-LIQUID CHROMATOGRAPHY.

Batardy-Gregoire M, Razzouk C, Evrard E, Roberfroid M
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Anal Biochem; 122(1):199-205 1982

An analytical procedure is described for quantitative estimation of the C5-and C7-hydroxylated metabolites of the carcinogenic amide, 2-fluorenylacetamide in the presence of rat or hamster liver microsomes and a NADPH-generating system. These metabolites were extracted and derivatized with heptofluorobutyrylimidazole. Subsequent analysis by gas-liquid chromatography with electron-capture detection was sensitive enough for determination of the kinetic parameters of these hydroxylation reactions. The effects of pretreatment with 3-methylcholanthrene or 2,3-benzanthracene on these parameters were also studied. (Author abstract) (24 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

32. CYTOSOLIC FACTORS IN THE MICROSOMAL METABOLISM OF DIMETHYLAMINOAZOBENZENE (DAB) (MEETING ABSTRACT)

Levine WG, Lee SB
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Fed Proc; 41(3):1730 1982

DAB is N-demethylated and ring hydroxylated by isozymes of cytochrome P-450. Microsomal metabolism of DAB is enhanced by the addition of cytosol; ring hydroxylation is increased to a much greater extent than is N-demethylation. Stimulation is seen both with an NADPH generating system and with added NADPH. The response is not due simply to the protein since added albumin has no effect. Stimulatory activity is partially removed by dialysis and by heating. Glutathione restores some of the activity lost during dialysis. Both cytosol and EDTA completely suppress microsomal lipid peroxidation but cytosol stimulates DAB metabolism to a much greater extent than does EDTA. Conjugation of metabolites is not a factor since there is no appreciable change in water-soluble metabolites upon addition of cytosol. Partial resolution of cytosolic proteins on a Bio-Gel column reveals stimulatory activity in the higher molecular size fractions and inhibitory activity in lower molecular size fractions. Conclusions: Multiple cytosolic factors affect DAB metabolism. Stimulation is partially heat labile, partially dialyzable. Effects on NADPH generation or formation of water-soluble conjugates are unlikely. Inhibition of lipid peroxidation is not a major factor. (no Refs)

33. TWO BIOLOGICAL REACTIVE INTERMEDIATES IN AMINOAZO-DYE CARCINOGENESIS AND THEIR GLUTATHIONE ADDUCTS.

Srai SK, Ketterer B, Kadlubar FF
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Adv Exp Med Biol; 136(partB):1297-1306 1982

Evidence is presented for the existence of two reactive intermediates of N,N-dimethyl-4-aminoazobenzene (DAB) and N,N-methyl-4-aminoazobenzene (MAB) and the role of their glutathione (GSH) adducts in the detoxification of aminoazo-dye carcinogens is discussed. The two intermediates apparently have different roles. N-sulfonoxy-N,N-methyl-4-aminoazobenzene (N-s-MAB), or its analogue N-benzoyloxy-N,N-methyl-4-aminoazobenzene (N-b-MAB), is a strong electrophile, is linked with carcinogenesis and mutagenesis, and forms DNA adducts. It must escape reaction with small molecular nucleophiles within the cell, particularly GSH, and GSH may have some limitations as a detoxifying agent for N-s-MAB. GSH trapped 40x as much N-s-MAB as did the macromolecular nucleophiles, demonstrating that it was much more effective in detoxification than the in vitro results suggested. N-methylol-4-aminoazobenzene (N-m-AB) was important in the detoxification of DAB since its GSH adduct, GS-CH2-AB, accounted for 20% of the total biliary excretion of DAB. Optimal excretion of DAB metabolites should depend on the maintenance of hepatic GSH levels. Depletion of hepatic GSH levels can be partly due to the selective inhibition of the formation and excretion of GS-CH2-AB. N-m-AB can also form adducts with thiols, phenols, and amines in nucleic acids; formation of adducts with macromolecules requires further study. (33 Refs)

34. PARTICIPATION OF THE MICROSOMAL ELECTRON TRANSPORT SYSTEM IN MUTAGENIC ACTIVATION OF 4-DIMETHYLAMINOAZOBENEZENE, 4-METHYLAMINOAZOBENZENE AND THEIR 3'-METHYL-DERIVATIVES.

Igarashi S, Yonekawa H, Kawajiri K, Watanabe J, Kimura T, Kodama M, Nagata C, Tagashira Y
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Biochem Biophys Res Commun; 106(1):164-169 1982

An antibody to NADPH-cytochrome P-450 reductase inhibited the mutagenic effect (measured by the Ames' assay) of 4-dimethylaminoazobenzene, 4-methylaminoazobenzene, and their 3'-methyl derivatives by 90%. The antibody against the 3-methylcholanthrene-inducible major P-450 (MC-P-448) inhibited the mutagenicity of these four compounds by 90% while the antibody against the phenobarbital-inducible major P-450 inhibited the mutagenicity by 20%. These results indicate that the microsomal electron transport system, in particular MC-P-448, is involved in the mutagenic activation of carcinogenic amino azo dyes. (28 Refs)

35. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT- AND INDIRECT-ACTING CARCINOGENS.

Nesnow S, Garland H, Curtis G
Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711
Carcinogenesis; 3(4):377-380 1982

Oncogenic transformation of C3H10T1/2CL8 cells was improved by treating the cells 5 days after seeding. Benzo[a]pyrene-induced transformation was increased 3.5-fold by this method, compared with treating the cells 1 day after seeding. N-Methyl-N'-nitro-N-nitrosoguanidine, which does not transform asynchronous cultures of C3H10T1/2CL8 cells when administered 1 day after seeding, produced an average of one focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and aflatoxin B1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. These results indicate the utility of this new procedure for the qualitative analysis of the transforming ability of chemicals. (Author abstract) (28 Refs)

36. THE SIGNIFICANCE OF CHOLANGIOFIBROSIS AS A 'PRENEOPLASTIC LESION' (MEETING ABSTRACT)

Evans JG, Conning DM, Appleby EC
The British Industrial Biological Research Association, Woodmansterne Road, Carshalton, Surrey, SM5 4DS, England
Toxicologist; 2(1):100 1982

The histogenesis of carcinoma of liver having an adenomatous or ductal pattern is uncertain. Many consider that such tumors arise from bile ducts and is preceded by cholangiofibrosis; others consider that they are histological variants of hepatocellular carcinoma. The changes produced in the liver of rats by 3'Methyl-4-diaminoazobenzene (3'MeDAB) and by coumarin are compared. 3'MeDAB administration led to extensive oval cell proliferation and then to cholangiofibrosis. This was followed by hepatic nodules with variable enzyme patterns and later, trabecular and adenomatous or duct carcinoma. Coumarin induced cholangiofibrosis in which four distinct stages could be recognized. No altered foci, areas or nodules were seen, and no hepatocellular tumors developed. The ultrastructure appearance of cholangiofibrosis was compared with that of adenomatous areas of carcinoma. Cells forming the lining epithelium in both were similar. Carcinomas with ductal or adenomatous pattern were deep within unequivocal hepatocellular carcinoma and it is considered that they represent variants of such tumors. Occasionally ductal tumors appeared to arise within cholangiofibrosis. Possibly proliferating ducts exposed to a carcinogen may be susceptible to neoplastic change. It is concluded that most of tumors, induced by 3'MeDAB, even those are variants of hepatocellular carcinoma. (no Refs)

HETEROCYCLIC AMINES

37. THE MUTAGENIC POTENTIAL OF: (E)-1,2,3,4-TETRAHYDRO-6-METHYL-1(2-METHYL-1-OXO-2 BUTENYL)QUINOLINE 1,2,3,4-TETRAHYDRO-6-METHYL-1-(3-METHYL-1-OXO-2 BUTENYL)QUINOLINE 50% DEET, 25% DOW CORNING 200 FLUID, IN ISOPROPANOL.

Sauers LJ, Pulliam FR, Frain JT
Letterman Army Inst. Res., San Francisco, CA
The Mutagenic Potential of: (E)-1,2,3,4-tetrahydro-6-methyl-1(2-methyl-1-oxo-2 butenyl)quinoline; 1,2,3,4-tetrahydro-6-methyl-1-(3-methyl-1-oxo-2 butenyl)quinoline; 50% DEET, 25% Dow Corning 200 Fluid, in Isopropanol. Available from National Technical Information Service, Springfield, VA, as AD-A107 628/0:, 33 pp., 1981.

The mutagenic potential of (E)-1,2,3,4-tetrahydro-6-methyl-1-(2-methyl-1-oxo-2 butenyl)quinoline (CHR5); 1,2,3,4-tetrahydro-6-methyl-1-(3-methyl-1-oxo-2 butenyl)quinoline (CHR6); 50% DEET, 25% Dow Corning 200 Fluid, in isopropanol (CHF1); was assessed using the Ames/Salmonella Mammalian Microsome Mutagenicity Assay. Tester strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, were exposed to 1 ul/plate through 0.000032 ul/plate doses of CHR5 and CHR6 and 0.1 ul/plate through 0.000032 ul/plate doses of CHF1. No evidence of mutagenic activity was observed. (Author abstract)

38. MORPHOLOGIC ANALYSIS OF ATYPICAL ACINAR CELL LESIONS (AACL) INDUCED IN RAT PANCREAS BY 4-HYDROXYAMINOQUINOLINE-1-OXIDE (4-HAQO) (MEETING ABSTRACT)

Rao MS, Upton MP, Subbarao V, Scarpelli DG
Department of Pathology, Northwestern University Medical, Chicago, IL, 60611
Fed Proc; 41(3):1547 1982

A metabolite of 4-nitroquinoline-1-oxide (4-HAQO), is both toxic and carcinogenic for pancreas. A single IV injection in male Wistar rats at a dose of 6 mg/kg bwt induced AACL in 100% of the animals. AACL could be classified histologically as zymogen-poor and zymogen-rich foci, and zymogen-rich nodules (grossly visible). The zymogen-poor foci contained 20-300 cells and rarely more than 500 cells. Cells in such foci were large, contained a large irregular nucleus with a prominent nucleolus, and a markedly basophilic cytoplasm with a few zymogen granules. By TEM (transmission electron microscopy) these cells showed markedly irregular lateral plasma membrane, and a well developed RER (rough endoplasmic reticulum). Cells in zymogen-rich foci and nodules were arranged in acini which were larger than adjacent ones, contained an intensely eosinophilic granular cytoplasm, and a large oval basophilic nucleus with a prominent nucleolus. These cells had a zymogen-rich cytoplasm, well developed RER, and irregular lateral membranes. Mitotic and [3H]thymidine labeling indices of both cell variants of AACL were as follows: eosinophilic cells, 2.75 and 23.2, basophilic cells 0.125 and 1.2 as compared to 0 to 1 for normal acinar cells. These studies indicate that 4-HAQO induces at least 2 variants of AACL with different morphological features and growth capacity. (no Refs)

39. STUDIES IN THE INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA MELANOGASTER BY NITROHETEROCYCLIC COMPOUNDS.

Kramers PG
Natl. Inst. Public Health, P.O. Box 1, Bilthoven, The Netherlands
Mutat Res; 101(3):209-236 1982

The induction of sex-linked recessive lethals in Drosophila melanogaster by 24 hr nitroheterocyclic compounds was investigated. The adult feeding technique was used in most cases, and injection and larval feeding in others. Of the nitroimidazoles tested, toxicity increased in the order metronidazole, nimorazole, ronidazole, dimetridazole. Among the nitrofurans, only nitrovin, furazolidone, and furaltadone were clearly mutagenic. Nitrofurantoin and niridazole were ambiguous. Nitrofurans were active at lower molar concentrations than were nitroimidazoles. 4-Nitroquinoline oxide was clearly mutagenic when fed to larvae. Drosophila gut flora were shown not to play role in the activation of ZK 26.173 and furazolidine to mutagenic metabolites. Activation of ZK 26.173 was significantly inhibited in Drosophila strains lacking xanthine dehydrogenase and aldehyde oxidase. (72 Refs)

40. EVIDENCE SUGGESTING THAT THE MECHANISM FOR AEROBIC AND HYPOXIC CYTOTOXICITY OF NITROHETEROCYCLES IS THE SAME.

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Int J Radiat Oncol Biol Phys; 8(3/4):687-691 1982

The fluorescence of three nitroheterocycles was used to measure the uptake and binding of the compounds by cells under hypoxic and aerobic conditions. Chinese hamster V-79 and mouse L-929 cells were exposed in suspension cultures to 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), trans-5-amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4 oxadiazole (AVO), or 4-nitroquinoline-1-oxide (4-NQO). Fluorescence was measured in single-cell samples by means of a fluorescence-activated cell sorter. Cellular fluorescence correlated with cell survival independently of the concentration of AF-2, time of exposure, or cell density, indicating that cell death was dependent on the amount of AF-2 taken in and bound by the cell. Higher concentrations of AF-2 in the medium were required for cell killing under aerobic conditions than under hypoxic conditions. However, at concentrations that produced equal toxicity, cellular fluorescence was similar under hypoxic and aerobic conditions. A correlation between cellular fluorescence and cell survival was also shown for 4-NQO. Incubation of V-79 cells with glutathione produced reductions in both toxicity and cellular fluorescence. Inhibition of DNA synthesis by AF-2 was independent of oxygen tension. Results suggest that the mechanism involved in cytotoxicity is the same under hypoxic and aerobic conditions. Oxygen evidently affects the rate of uptake of nitroheterocycles, rather than the nature of the toxic species. The toxic species is most likely the nitro anion radical. (18 Refs)

41. MUTAGENIC ACTIVITY OF THREE ISOMERIC N-NITROSO-N-METHYLAMINO-PYRIDINES TOWARDS ESCHERICHIA COLI K-12 IN IN VITRO AND ANIMAL-MEDIATED ASSAYS.

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Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, The Netherlands
Carcinogenesis; 3(4):415-421 1982

Three isomeric nitrosomethylaminopyridines were tested in vitro and in the host-mediated assay for their activity to induce gene mutations in E coli K-12 strain 343/113. Nitrosodimethylamine (NDMA) and nitrosomethylaniline (NMA) were also tested. The in vitro mutagenicity tests were performed either without in the presence of various fractions (S-9, microsomes, S-100) of rodent liver homogenates. The in vivo mutagenicity was determined in host-mediated assays, in which the indicator E coli cells were recovered for the liver of treated animals. N-nitro-N-methyl-2-aminopyridine (2-NMPY) and N-nitro-N-methyl-4-aminopyridine (4-NMPY) were activated to mutagenic factors by microsomes, but their mutagenic effect was completely abolished when S-100 was added. N-nitro-N-methyl-3-aminopyridine (3-NMPY) was directly mutagenic for E coli but its mutagenic potential was abolished when S-100 liver fraction was added to the incubation mixtures. NDMA was activated to mutagenic factors with both microsomes and S-9 fractions, whereas NMA could not be shown as mutagenically active under any of the present experimental conditions. It could be shown that the deactivating effect of the S-100 fraction was of non-enzymatic nature, and probably was due to the presence of thiol-containing 'scavenger' molecules in this fraction. In the host-mediated assays, only the 2-isomer among the three exerted a mutagenic affect. The results indicate that the isomers investigated here are mutagenic either directly or upon microsomal activation. The non-carcinogenicity of 3-NMPY and 4-NMPY, and the non-mutagenicity of these compounds in host-mediated assays, is probably the result of very efficient deactivation by cytosolic (thiol-group-containing?) factors. (23 Refs)

42. IN VITRO ENZYMATIC RECOGNITION OF DNA MODIFIED BY O,O'-DIACETYL OR O-ACETYL DERIVATIVES OF THE CARCINOGEN 4-HYDROXYAMINOQUINOLINE-1-OXIDE.

Gallegue S, Bailleul B, Loucheux-Lefebvre MH, Laval J

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Carcinogenesis; 3(4):435-438 1982

Purified DNA was modified in vitro by 3H-labeled O-acetyl or O,O'-diacetyl-4-hydroxyaminoquinoline-1-oxide (Ac-4HAQO or diAc-4HAQO). It was then subjected to the action of the single-stranded DNA specific nuclease S1 and the digested fractions were analyzed. For both types of modified DNA, the release of non-modified nucleotides was faster than the release of modified nucleotides. This result is at variance with that obtained with acetoxy-acetylaminofluorene-modified DNA: in the latter case, the modified nucleotides were preferentially released. The results suggest that the S1 endonuclease can recognize different conformational changes in DNA, which depend on the carcinogen used. The enzymatic activity (or activities) present in Micrococcus luteus cell extracts released ethanol-soluble products from Ac-4HAQO modified DNA. (Author abstract) (24 Refs)

43. MAMMALIAN CELL POINT MUTATION ASSAY WITH THE ANTINEOPLASTIC AMSACRINE (MEETING ABSTRACT)

Lake RS, McGuire EJ, De la Iglesia FA

Department of Toxicology, Warner-Lambert/Park-Davis Pharmaceutical Research Division, Ann Arbor, MI, 48105

Toxicologist; 2(1):173 1982

A battery of short-term in vitro tests was designed for evaluating carcinogenesis potential of the antineoplastic agent amsacrine, an acridinylamino anisidine derivative. Previous genotoxicity assays showed frameshift mutagenesis at the hisC3076 locus in Salmonella TA-1537 but no confirmed mutagenesis in TA-98, TA-100, TA-1535, and TA-1538. In Chinese hamster ovary cell assays, amsacrine induced sister-chromatid exchanges and hyperdiploid chromosomes. There are no data available on mammalian point mutation with amsacrine and a V-79 Chinese hamster lung cells assay was conducted to detect HGPRT (hypoxanthine guanine-phosphoribosyltransferase) locus mutation. Cytotoxicity was established at 2 ug/ml and one hour exposures were used with 2, 1, 0.5 and 0.25 ug drug/ml in duplicate flasks. Positive control was ethylmethane sulfonate at 800 ug/ml. Lethality occurred at 2 and 1 ug/ml. A significant number of 6-thioguanine resistant mutant colonies were induced at 0.5 and 0.25 ug/ml. The results indicate high mutagen sensitivity of this assay when compared to the dose required to induce reverse mutation in prokaryotes with a 1,000-fold separation in minimum effective dose. The evaluation of the battery of tests conducted unequivocally render a genotoxic potential. (no Refs)

44. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

Lenk W, Scharmer U
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Adv Exp Med Biol; 136(partB):951-970 1982

Experiments on the metabolic fate of N-hydroxy-4-chloroacetanilide (N-OH-4ClAA), N-hydroxy-2-acetylaminofluorene (N-OH-2AAF), N-hydroxy-4-acetylaminobiphenyl (N-OH-4AAB), and N-hydroxyphenacetin (NHP) in rabbit or rat liver microsomal and cytosolic systems are reviewed. Differences in substrate affinity cause microsomal and cytosolic N-OH-2AAF, N-OH-4AAB, N-OH-4ClAA, and NHP to be N-deacylated at different rates, but the differences are not clear-cut enough to permit differentiation between carcinogenic polycyclic and noncarcinogenic monocyclic compounds. Differences in the rates of oxidation of the corresponding arylhydroxyamines were also detected, but these were likewise not clear enough for separation of respective poly- and monocyclic compounds. Clear differences in reactivity between poly- and monocyclic nitrosoarenes were observed, but have not been related to toxicity of the corresponding N-arylacetohydroxamic acids. The prominent reactivity of N-OH-2AAF and of 2-nitrosofluorene suggests that the primary lesion, from which tumor growth is initiated, may be caused by this arylhydroxylamine and/or its N-arylacetohydroxamic acid. (38 Refs)

45. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS.

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Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
JOM; 24(5):369-374 1982

Genetic traits that may predispose individuals to occupational diseases are reviewed. A single-gene difference affecting N-acetyl-transferase (NAT) activity in liver makes individuals slow acetylators (recessive) or rapid acetylators (dominant) of a series clinically important drugs. NAT is known to be involved in acetylation and thus inactivation arylamines that are potent bladder carcinogens, including beta-naphthylamine, benzidine, 4-amino-biphenyl, and 4-nitrobiphenyl, all of which are used as industrial oxidants. An excess of slow acetylators has been observed in groups with a high incidence of occupational bladder cancers. Genetic control of microsomal oxidizing systems appears to be related to certain occupational disease. Aryl hydrocarbon hydroxylase (AHH) has been shown to be involved in activating many promutagenic and procarcinogenic aryl hydrocarbons, of which benzopyrene is the prototype. The pesticide parathion and its active metabolite paraoxon are inactivated by plasma paraoxonase. Potential genetic predispositions due to differences in tissue sensitivity include the following: hemolysis due to glucose-6-phosphodiesterase; sickle cell trait; plasma alpha-antitrypsin deficiency and pulmonary emphysema; low-back pain, ankylosing spondylitis, and histocompatibility antigen B27; and skin hypersensitivity reactions. Opportunities for research/criteria for development of screening tests are discussed. (35 Refs)

46. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

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Adv Exp Med Biol; 136(partA):555-573 1982

Studies concerning the capacity of placental tissues to biotransform and bioactivate polycyclic aromatic hydrocarbons (PAH) and the placental enzyme systems that catalyze these reactions are reviewed. PAH which undergo enzymically-catalyzed monooxygenation in placental tissues include: benzo(a)pyrene (BaP), 7,12-dimethylbenz(a)anthracene (DMBA), N-2-fluorenylacetamide (FAA), 3-methylcholanthrene (3MC), chrysene, benzo(e)pyrene, dibenz(a,h)anthracene and benz(a)anthracene. For each of these substrates, hydroxylation rates are increased by preexposure of the maternal organism to 3MC, but not to phenobarbital-type inducers. Placental enzymes can catalyze the conversion of at least three of these substrates (DMBA, BaP and FAA) to reactive intermediates. Recent studies indicate that a number of P-450 cytochromes that are not spectrally detectable with current methods are responsible for the limited bioactivation observed. 3MC- and phenobarbital-inducible monooxygenases also catalyze the conversion of estrogens to catechol estrogens in placental tissues of humans and experimental animals. The in vivo significance of these observations remains to be clarified. (52 Refs)

47. METABOLISM OF CHEMICAL CARCINOGENS.

Weisburger JH, Williams G
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Chemical carcinogens are defined by their ability to induce tumors, four types of response have generally been accepted as evidence of tumorigenicity. These include an increased incidence of the tumor types occurring in controls, the occurrence of tumors earlier than in controls, the development of types of tumors not seen in controls, and an increased multiplicity of tumors in individual animals. Examples of the genotoxic carcinogen class include alkylating agents which are activation independent, aromatic amines and polycyclic aromatic hydrocarbons which are activation-dependent, and metals. Examples of the epigenetic carcinogen class include plastics and asbestos, estrogen, androgen, purine analog, and phorbol ester. Promotors are agents that increase the tumorigenic response to a carcinogen when applied after the carcinogen. Genetic factors, sex and endocrine status, age, diet, activities of intestinal flora, the presence of other chemicals, the mode and frequency of exposure, and numerous other factors influence the variation in carcinogen metabolism. Research during the last few decades has pinpointed natural products as major causes of cancer in humans in various parts of the world. (486 Refs)

48. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Purine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in chromatin. Interactions of chemical carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to urethan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

49. SEQUENTIAL ASPECTS OF CHEMICAL CARCINOGENESIS: SKIN.

Berenblum I
Weizmann Inst. Science, Rehovot, Israel
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The two-stage hypothesis, the initiation-promotion hypothesis, was based on animal studies of sequential stages of skin carcinogenesis. Initiators for skin carcinogenesis include 2-acetylaminofluorene, UV light, beta-radiation, certain metabolites of 'complete' carcinogens, various alkylating agents and mutagens. Promoters for skin carcinogenesis include physical agents, 'complete' chemical carcinogens, non- or weakly-acting skin carcinogens, croton oil, straight-chain N-alkanes, phenolic compounds, extracts of tobacco leaf, and extracts of tobacco smoke condensates. The two-stage system in skin carcinogenesis has been extended, based on further experiments. Evidence that a mutational change in the DNA genome was responsible for the initiating change of carcinogenesis is based on the ability of most carcinogens to bind with DNA and that there is a fairly good correlation between mutagenic and carcinogenic properties among a wide range of compounds. Evidence for the stimulation of synthetic processes in the cell includes the stimulation of DNA and RNA synthesis as well as protein and phospholipid synthesis. The effects of enzymatic functions in the cell are based on an increase in proteinase activity, on stimulation of ornithine decarboxylase activity, on changes in cyclic nucleotide levels, and on a decrease in histidase activity. (378 Refs)

50. NEOANTIGEN EXPRESSION IN CHEMICAL CARCINOGENESIS.

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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Neoantigens have been found on tumors which were chemically induced by polycyclic hydrocarbons, by aminoazo dyes, by aromatic amines, by alkylnitrosamines, and by hydrazines. Several findings are consistent with the view that tumor-associated antigens on chemically induced tumors are expressed on integral membrane proteins or glycoproteins. Attempts to develop cell-free radioimmunoassays for these antigens have generally been unsuccessful. One of the major problems has been to retain the capacity of the radiolabeled antigens to rebind with antibodies in syngeneic immune sera. The significance of the possible relationships between tumor-associated neoantigens and products of major histocompatibility complex needs to be further evaluated. Oncodevelopmental antigens appear to be associated with numerous types of chemically induced tumors, and thus they should be regarded as valuable potential markers for studying transformation-related events. Three possible pathways leading to neoantigen expression include their appearance as a consequence of early interactions of carcinogen with target cells, their expression which only occurs once the initiated cell is converted to the preneoplastic cell, and their expression at the stage when malignant cell clones develop. (328 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer G
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
In GER

3. NITROSAMINES.
Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982
In GER

4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982
In RUS

5. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.
Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982
In CZE

6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
Burke L
Obstetrics/Gynecology Dept., Harvard Medical Sch., Boston, MA
Curr Probl Obstet Gynecol; 5(2):1-58 1981

7. IN UTERO EXPOSURE TO DIETHYLSTILBESTROL: ADVERSE EFFECTS ON THE REPRODUCTIVE TRACT AND REPRODUCTIVE PERFORMANCE IN MALE AND FEMALE OFFSPRING.
Stillman RJ
Dept. Obstetrics and Gynecology, George Washington Univ. Sch. Medicine and Health Sciences, 2150 Pennsylvania Ave., NW, Washington, DC, 20037
Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrborn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
Socialmedicinsk institut, Vesterbro Torv 1-3, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(13):971-975 1982
In DAN

DIETARY FACTORS IN CARCINOGENESIS

9. NATURALLY OCCURRING FOOD TOXICANTS: PHENOLIC SUBSTANCES OF PLANT ORIGIN COMMON IN FOODS.
Singleton VL
Dept. Viticulture and Enology, Univ. California, Davis, CA
Adv Food Res; 27:149-242 1981

10. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.
Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer; 49(10):1970-1984 1982

11. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.
Larsen B
Kraeftforskningsinstituttet, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(12):860-863 1982
In DAN

12. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.
Sivak A, Rudenko L, Teague LG
Arthur D. Little, Inc., Cambridge, MA, 02140
Environ Mutagen; 4(2):143-162 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

13. CANCER IN THAILAND: LESSONS FOR CANCER CONTROL.
Miller DG, Sombooncharoen S
Strang Clinic, Preventive Medicine Inst., 55 East 34th St., New York, NY, 10016
Prev Med; 11(2):232-239 1982

14. MEASUREMENT OF CANCER INCIDENCE IN THE UNITED STATES: SOURCES AND USES OF DATA.
Greenberg ER, Colton T, Bagne C
Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Hanover, NH, 03755
JNCI; 68(5):743-750 1982

15. STUDIES OF CANCER EPIDEMIOLOGY IN THE UNITED STATES OF AMERICA.
Lapin IuE
Moscow, USSR
Feldsher Akush; (2):55-57 1982
In RUS

16. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.
Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982
In RUS

17. ETIOLOGY OF MOUTH AND LIP TUMORS.
Zabezhinskii MA, Godorozha PD
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 28(2):105-113 1982
In RUS

18. PSYCHIATRIC ASPECTS OF CANCER.
Peterson LG, Popkin MK, Hall RC
P.O. Box 20708, 6431 Fannin, Houston, TX, 77025
Psychosomatics; 22(9):774-793 1981

19. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS.
Omenn GS
Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
JOM; 24(5):369-374 1982

20. CARCINOGENESIS AND CURRENT HYPOTHESIS ON THE TUMOR-HOST INTERACTIONS.
Neiman IM
No affiliation given
Patol Fiziol Eksp Ter; (2):63-70 1981
In RUS

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

21. POLYCHLORINATED BIPHENYLS (PCBS): AN AUSTRALIAN VIEWPOINT ON A GLOBAL PROBLEM.
Richardson BJ, Waid JS
Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
Search; 13(1/2):17-25 1982

22. SIGNIFICANCE OF ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF LEUKEMIA, MYELOMA AND MALIGNANT LYMPHOMA.
Brandt L
Onkologiska kliniken, Lasarettet, Lund, Sweden
Lakartidningen; 79(15):1490-1492 1982
In SWE

23. ENVIRONMENTAL FACTORS AND MALIGNANT HEMATOLOGICAL DISEASES.
Bjorkholm M
Hematologsektionen, Danderyds sjukhus, Danderyd, Sweden
Lakartidningen; 79(15):1457-1459 1982
In SWE

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida, Coll. Medicine, Gainesville, FL, 32610
Pathobiol Annu; 11:1-29 1981

25. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?
Weinhouse S
Fels Res. Inst., Temple Univ. Sch. Medicine, Health Sciences Center, Philadelphia, PA, 19140
JNCI; 68(3):343-349 1982

26. CHANGES IN AMINO ACID AND SUGAR TRANSPORT ACTIVITY ASSOCIATED WITH MALIGNANT TRANSFORMATION.
Nishino H, Iwai K
Dept. Biochemistry, Kyoto Prefectural Medical Univ., Kyoto, Japan
Tanpakushitsu Kakusan Koso; 26(7):881-895 1981
In JPN

27. CURRENT VIEWS ON THE NATURE OF MYOEPITHELIAL CELLS AND THEIR ROLE IN THE MORPHOGENESIS OF DYSHORMONAL HYPERPLASIAS AND BREAST TUMORS.
Karelina TV
Central Lab. Pathology, Inst. Human Morphology, Moscow, USSR
Arkh Patol; 44(2):69-73 1982
In RUS

MODIFICATION OF CARCINOGENESIS

28. OVERVIEW: RETINOIDS AND CARCINOGENESIS.
Schramm T, Coutelle R
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(4):323-336 1982
In GER

29. RETINOIDS, URINARY BLADDER CARCINOGENESIS, AND CHEMOPREVENTION: A REVIEW AND SYNTHESIS.
Lower GM, Kanarek MS
Dept. Veterinary Science, Coll. Agricultural and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
Nutr Cancer; 3(2):109-115 1981

30. THE ANTITUMOR POLYSACCHARIDE LENTINAN: AN OVERVIEW.
Chihara G
Natl. Cancer Res. Inst., Tsukiji, Tokyo, Japan
Excerpta Med Int Congr Ser; 576:1-16 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ENDOGENOUS ONCOGENIC TYPE B VIRUSES IN MICE.
Komarova EA, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):3-12 1982
In RUS

32. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.
Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

33. THE PERSISTENCE OF RETROVIRUSES.
Weiss RA
Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England
Symp Soc Gen Microbiol; 33:267-288 1982

34. HOW DO PAPOVA VIRUSES PERSIST IN THEIR HOSTS?
Griffin BE
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Symp Soc Gen Microbiol; 33:227-247 1982

35. THE EPSTEIN-BARR VIRUS: HISTORICAL, BIOLOGIC, PATHOLOGIC AND ONCOLOGIC CONSIDERATIONS.
Seemayer TA, Oligny LL, Gartner JG
Dept. Pathology, Montreal Children's Hosp., Montreal, Quebec, Canada
Perspect Pediatr Pathol; 6:1-33 1981

36. KAPOSI'S SARCOMA: WHY A 'HOMOSEXUAL DISEASE'?
Groopman JE, Gottlieb MS
Div. Hematology-Oncology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA
Hosp Pract; 17(5):64F-64G,64J,64N,64O,64R,64T 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

37. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.
Plisa GB, Turusov VS, Zabezhinskii MA
No affiliation given
Vopr Onkol; 28(2):18-22 1982
In RUS

38. ON THE NECESSITY OF MUTAGENICITY TESTING OF NEW DRUGS.
Bogajewski J, Schoneich J
Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland
Pol Tyg Lek; 37(2):63-67 1982
In POL

OTHER REVIEWS IN CARCINOGENESIS

39. CANCER - PRINCIPLES AND PRACTICE OF ONCOLOGY.
DeVita VT, Hellman S, Rosenberg SA

NCI, Bethesda, MD
Cancer - Principles and Practice of Oncology. Philadelphia, Lippincott, 1526 pp., 1982.

40. MOVABLE GENETIC ELEMENTS.
Watson JD
Cold Spring Harbor Lab., Box 100, Cold Spring Harbor, NY, 11724
Cold Spring Harbor Symp Quant Biol 45(part 1): 445 pp., 1981.

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ICRDB CANCERGRAM

CHEMICAL CARCINOGENESIS

Azo Dyes, Aryl Amines, and Related Compounds

SERIES CK10 No. 82/11

NOVEMBER, 1982

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ANILINES AND EXTENDED ANILINES

1. COVALENT BINDING OF BENZIDINE AND N-ACETYLBENZIDINE TO DNA AT THE C-8 ATOM OF DEOXYGUANOSINE IN VIVO AND IN VITRO.

Martin CN, Beland FA, Roth RW, Kadlubar FF
Cancer Res. Unit, Univ. York, York YO1 5DD, England
Cancer Res; 42(7):2678-2686 1982

Benzidine, a human urinary bladder carcinogen, induces hepatic tumors in mice and rats. In this study [3H]benzidine was administered in drinking water to mice for 1 wk, and the covalent binding of the carcinogen to hepatic DNA was then determined. A single carcinogen: DNA adduct was detected which decreased in concentration by approx 50% at 1 day after treatment and then remained at a nearly constant level for at least 7 days. Injection of radiolabeled benzidine or N-acetylbenzidine into rats also resulted in a single carcinogen:DNA adduct that was chromatographically identical to that obtained in mouse liver. While administration of benzidine and N-acetylbenzidine resulted in high levels of the adduct in rat hepatic DNA, injection of N,N'-[ring-14C]diacetylbenzidine did not give detectable binding. The same carcinogen:DNA adduct found in rat

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and mouse liver was prepared synthetically by: (a) hydrolysis of calf thymus DNA reacted with N-hydroxy-N'-acetylbenzidine at pH 5; and (b) reaction of N-acetoxy-N,N'-diacetylbenzidine with deoxyguanosine and subsequent selective deacetylation of the product with methanolic ammonia. Mass and nuclear magnetic resonance spectral data of the synthetic products established the structure of the hepatic adduct as N-(deoxyguanosin-8-yl)-N'-acetylbenzidine. The nonacetylated derivative, N-(deoxyguanosin-8-yl)benzidine, was synthesized by carboxylesterase treatment of N-(deoxyguanosin-8-yl)-N'-acetylbenzidine and was shown not to occur in rat and mouse liver DNA. These data indicate that the metabolic activation of benzidine to an ultimate carcinogen in rats and mice does not involve N-hydroxybenzidine or sulfotransferase-catalyzed activation of N-hydroxy-N,N'-diacetylbenzidine. The remaining pathways for metabolic conversion of benzidine to an ultimate carcinogenic species are discussed in relation to liver and urinary bladder carcinogenesis. (46 Refs)

2. DIFFERENTIAL ABILITY OF AMBYSTOMA TIGRINUM HEPATIC MICROSOMES TO PRODUCE MUTAGENIC METABOLITES FROM POLYCYCLIC AROMATIC HYDROCARBONS AND AROMATIC AMINES.

Anderson RS, Doos JE, Rose FL
Sloan Kettering Inst. Cancer Res., 145 Boston Post Road, Rye, NY, 10580
Cancer Lett; 16(1):33-41 1982

The ability of salamander hepatic microsomal mixed function oxygenases to metabolize benzo(a)pyrene (BP), perylene and the aromatic amines 2-aminoanthracene (AA), 2-aminofluorene (AF), 2-acetylaminofluorene (AAF), 4-amino-trans-stilbene (AS), monoacetylbenzidene (MAB), and diacetylbenzidine (DAB), to chemical species capable of inducing revertants in Salmonella typhimurium was investigated. Microsomal enzyme preparations from the livers of Aroclor-induced salamanders mediated the activation of AA, AF, AAF, AS, MAB, and DAB. Benzidene and 4-aminobiphenyl were poorly mutagenic in this system. The reactions were NADPH- and microsomal enzyme concentration-dependent. Rat microsomal enzyme induction with phenobarbital produced a marked increased in mutagenesis by benzidine, MAB, and DAB. However, phenobarbital was not a more effective inducer than Aroclor in the activation of these or other tested aromatic amines by salamander enzymes. No evidence was observed that BP or perylene were mutagenic after reaction with salamander liver microsomes. It is suggested that amphibian microsomal oxygenases may carry out N-oxidation more efficiently than C-oxidation. (30 Refs)

3. COMPARATIVE CARCINOGENICITY OF O-TOLUIDINE HYDROCHLORIDE AND O-NITROSOTOLUENE IN F-344 RATS.

Hecht SS, El-Bayoumy K, Rivenson A, Fiala E
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Lett; 16(1):103-108 1982

The carcinogenicity of o-toluidine hydrochloride (TOL) and o-nitrosotoluene (NTOL) in F-344 rats was evaluated. Mean weights were somewhat lower in the TOL and NTOL groups than in the control group. The mean daily doses of TOL and of NTOL (administered in the diet) were 0.062 g and 0.051 g, respectively. Food consumption was slightly less in the treated animals than in the animals fed the control diet. NTOL was significantly more effective than TOL in inducing hepatomas and bladder papillomas but was less active in the induction of mammary fibroadenomas. Both compounds induced significant numbers of fibromas of the skin and spleen as well as peritoneal tumors. The sc tumors were fibromas or mammary fibroadenomas. The peritoneal tumors were mesotheliomas and low grade spindle cell sarcomas. All invaded deeply into various abdominal organs and the muscular wall of the cavity. Most liver tumors were highly malignant hepatocarcinomas. Two rats displayed enormous multiple metastases of hepatoma tissue to the lungs. Bladder and pelvis-of-kidney tumors were of the usual transitional epithelium type. These results suggest that N-oxidation is important in the induction of bladder and liver tumors, while other metabolic conversions may play a role in the induction of other tumor types observed. (15 Refs)

4. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME AROMATIC AMINES, ANTHRAQUINONES AND NITROSO COMPOUNDS, AND INORGANIC FLUORIDES USED IN DRINKING-WATER AND DENTAL PREPARATIONS.

IARC Working Group
International Agency for Research on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 27:1-7 1982

Monographs on carcinogenicity data for groups of chemicals to which humans are known to be exposed are presented, and some aromatic amines and anthraquinones (used mainly as dyestuff intermediates), two nitroso compounds, and inorganic fluorides used in the fluoridation of drinking water or in dental preparations are included. The importance of data on the purity of chemicals used in animal carcinogenicity experiments and in mutagenicity tests was emphasized. Aromatic amines discussed include aniline and aniline hydrochloride, ortho-anisidine and para-anisidine and their hydrochlorides, 4-chloro-ortho-phenylenediamine and 4-chloro-meta-phenylenediamine, meta-cresidine and para-cresidine, 2,4-diaminoanisole and 2,4-diaminoanisole sulfate, 4,4'-methylenebis(N,N-dimethyl)benzenamine, 1,5-naphthalenediamine, 2,2',5,5'-tetrachlorobenzidine, 4,4'-thiodianiline, ortho-toluidine and ortho-toluidine hydrochloride, and 2,4,5-trimethylaniline and 2,4,6-trimethylaniline and their hydrochlorides. Anthraquinones include 2-aminoanthraquinone, 1-amino-2-methylanthraquinone, and 2-methyl-1-nitroanthraquinone. Nitroso compounds include N-nitrosodiphenylamine and para-nitrosodiphenylamine. An appendix on the epidemiological evidence relating to the possible carcinogenic effects of hair dyes in hairdressers and users of hair dyes is included. Critical analyses of the data presented are made in order to assist national and international authorities in formulating decisions concerning preventive measures. (744 Refs)

FLUORENAMINES: IN VIVO

5. EFFECT OF CARBON TETRACHLORIDE ON THE INDUCTION AND DEVELOPMENT OF HEPATOMA INDUCED BY 2-N-ACETYLAMINOFLUORENE IN INBRED WISTAR RATS.

Szydlo Z
Zaklad Anatomii Patologicznej, Instytut Biostruktury AM, ul. Pilata 5, 51-605 Wroclaw, Poland
Patol Pol; 32(4):471-486 1981

The effect of carbon tetrachloride (CT) on histological changes induced by 2-N-acetylaminofluorene (AAF) in the livers of 3-mo-old inbred male and female Wistar rats was studied. The substances were administered simultaneously through gastric probes for 3-5 mo at which time some of the animals were decapitated. The hepatic lesions were found to be more pronounced in the group treated with CT only (0.2 ml/day) than in those treated with AAF only (15 mg/day). Focal nodular hyperplasia was found in both groups at mo 5 but not at mo 3. Benign or malignant multifocal hepatomas were found in all animals decapitated after 5-mo treatment with both CT (2 ml) and AAF (15 ml), but only multifocal benign hepatomas or focal nodular hyperplasia were found in the animals decapitated after 3 mo of treatment. Multifocal benign hepatomas and focal nodular hyperplasia were found in another group treated with reduced doses of CT (0.1 ml/day) and AAF (7.5 mg/day) for 3 mo, and all animals treated with such doses for 5 mo developed multifocal benign hepatomas. The findings indicated that the hepatic changes observed were a combination of the lesions induced by the two substances. (28 Refs) (In POL)

6. SEQUENTIAL 2-ACETYLAMINOFLUORENE-PHENOBARBITAL EXPOSURE INDUCES A CYTOSOLIC ALDEHYDE DEHYDROGENASE DURING RAT HEPATOCARCINOGENESIS.

Allen B, Lindahl R
(c/o Lindahl) Biochemistry Program, Dept. Biology, Univ. Alabama, University, AL, 35486
Carcinogenesis; 3(5):533-538 1982

A significant change in hepatic aldehyde dehydrogenase activity has been observed in normal Sprague-Dawley rat liver during the promotion phase of hepatocarcinogenesis induced by brief feeding of 2-acetylaminofluorene (2-AAF) followed by tumor promotion using dietary phenobarbital (PB) exposure. Animals receiving only 2-AAF or PB do not possess this new aldehyde dehydrogenase activity. The phenotype is characterized by the appearance of a new cytosolic isozyme kinetically, electrophoretically and immunochemically distinct from the normal liver aldehyde dehydrogenase isozymes and from aldehyde dehydrogenases inducible in 2-AAF-induced hepatomas. The new isozyme is NAD-dependent, disulfiram-sensitive and cross-reacts with antiserum to a normal liver aldehyde dehydrogenase inducible in several lines of rats by PB. However, the population of animals used in this study has been shown previously to be non-responsive to aldehyde dehydrogenase induction by dietary PB. Since no animals receiving only PB express this new isozyme, the carcinogen must play a significant role in its induction. Moreover, that not all animals receiving carcinogen and promoter possess the phenotype suggests this carcinogen/promoter interaction has a genetic basis. (Author abstract) (19 Refs)

7. ON THE LIKELY MECHANISMS BY WHICH CARCINOGENS INDUCED ADRIAMYCIN RESISTANCE IN RAT HEPATOCYTES (MEETING ABSTRACT)

Carr BI, Langley DB
Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA, 91010
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

Administration of the hepatocarcinogen 2-acetylaminofluorene (AFF) to rats induces a resistance in their hepatocytes to doses of adriamycin (Ad) that are cytocidal to normal hepatocytes after incubation in vitro in primary monolayer culture. To investigate the mechanism of this carcinogen-induced resistance, sensitive (normal) and resistant (2-AAF altered) hepatocytes were incubated with Ad 1.8 x 10-5M for periods up to 24 hrs. No differences were observed in the cellular uptake, efflux, DNA-binding, DNA nicks, or inactive Ad aglycone metabolites between sensitive and resistant cells. However, only 50% of the fluorescing material was organic extractable. Examination of the aqueous non-extractable material revealed that this comprised 13% of the total cellular fluorescence in the sensitive cells and 34% in the resistant cells. It contained mainly highly polar metabolites, presumably water-soluble conjugates. Administration of Ad mg/kg iv to normal or 2-AAF treated rats resulted in similar concentrations of Ad and % fluorescence in the non-toxic aglycone metabolites. No Ad-OH was observed. (1 Ref)

8. CLONAL GROWTH OF CARCINOGEN-INDUCED ENZYME-DEFICIENT PRENEOPLASTIC CELL POPULATIONS IN MOUSE LIVER.

Rabes HM, Bucher T, Hartmann A, Linke I, Dunnwald M
Pathologisches Institut, Universitat Munchen, Munich 2, W. Germany
Cancer Res; 42(8):3220-3227 1982

The cellular origin of preneoplastic subpopulations in liver during chemical carcinogenesis has not yet been clarified. An experimental approach to this problem became possible by using female phenotypic mosaics caused by the X-chromosome inactivation ('lyonization') occurring early in embryogenesis. Allozymes of the X-linked enzyme phosphoglycerate kinase (PGK-1) served as markers of the maternal (wild-type PGK-1B) and paternal (variant PGK-1A) X-chromosomes in crosses of near-congenic C3H mice. These PGK allozymes are of similar activity and stability but can be separated electrophoretically and quantified by a fluorimetric method. Pgk-1a/Pgk-1b heterozygous females were subjected to chronic 2-acetylaminofluorene feeding for up to 14 mo. Phenotypic expression of PGK-1B and PGK-1A was determined in ug samples as well as in mg samples of liver and other organs. Samples of adenosine triphosphatase-deficient preneoplastic populations punched out from cryostat serial sections of liver of 2-acetylaminofluorene-fed mice disclosed a PGK allozyme pattern strikingly different from the norm. Thirty-nine of 40 preneoplastic nodules contained a pure population of either PGK-1A or PGK-1B expressing cells. Mean contamination by the opposite PGK type was 1.1%. In all cases, the PGK expression in the preneoplastic nodules differed from the surrounding liver parenchyma. Only a single large hyperplastic nodule was composed of several subpopulations with respect to PGK expression. Determination in normal liver tissue of the patch size of coherent populations with a homogeneous expression of one PGK allozyme revealed an av of about eight hepatocytes per patch. Each microsample used for PGK determinations consisted of an av of 25 patches. It is evident from these results that AAF-induced, ATPase-deficient preneoplastic subpopulations in the mouse liver are in all probability clones derived from a single cell. (Author abstract) (43 Refs)

FLUORENAMINES: IN VITRO

9. CYTOCHROME P-450-AND FLAVIN-CONTAINING MONOOXYGENASE-CATALYZED FORMATION OF THE CARCINOGEN N-HYDROXY-2-AMINOFLUORENE AND ITS COVALENT BINDING TO NUCLEAR DNA.

Frederick CB, Mays JB, Ziegler DM, Guengerich FP, Kadlubar FF (c/o Kadlubar) Natl. Center for Toxicological Res., Food and Drug Admin., Environmental Protection Agency, Jefferson, AR, 72079
Cancer Res; 42(7):2671-2677 1982

The metabolic N-oxidation of the carcinogen 2-aminofluorene was examined in vitro using fortified hepatic microsomes from a variety of species. Rat, dog, human, and pig liver microsomes catalyzed the formation of N-hydroxy-2-aminofluorene (N-OH-AF) from AF at rates of 1.6, 1.0, 1.2, and 3.5 nmol/min/mg protein, respectively. The involvement of both cytochrome P-450 and the flavin-containing monooxygenase was demonstrated with hepatic microsomes and with purified enzymes by using specific enzyme inhibitors. 2-[(2,4-Dichloro-6-phenyl)phenoxy]ethylamine, a potent cytochrome P-450 inhibitor, decreased microsomal N-OH-AF formation by 96, 83, 70, and 46% in the rat, dog, human, and pig, respectively; and further addition of methimazole, a high-affinity flavin-containing monooxygenase substrate, abolished the residual N-hydroxylating activity. Using the purified porcine flavin-containing monooxygenase, metabolic formation of N-OH-AF occurred at a rate of 4.9 nmol/min/nmol flavin adenine dinucleotide and was insensitive to 2-[(2,4-dichloro-6-phenyl)phenoxy]ethylamine inhibition. In addition, purified rat liver cytochrome P-450 (isolated from 5,6-naphthoflavone-induced animals) N-hydroxylated AF (1.1 nmol/min/nmol P-450) and was completely inhibited by 2-[(2,4-dichloro-6-phenyl)-phenoxy]ethylamine, but the reaction was insensitive to methimazole. To determine whether or not the metabolic formation of N-OH-AF could lead directly to covalently bound adduct(s) with DNA under these incubation conditions (30 min, pH 7.5), the binding of synthetic and metabolically formed [3H]-N-OH-AF to added calf thymus DNA and to DNA in isolated rat liver nuclei was investigated. In all cases, the amount of DNA-bound carcinogen accounted for 0.08 to 0.15% of the N-OH-AF present in the incubation mixtures. These data, when compared to the levels of AF bound to hepatic nuclear DNA reported in vivo, suggest that the nonenzymatic reaction of N-OH-AF with nuclear DNA may be sufficient to account for a substantial portion of the observed in vivo binding of this carcinogen. (Author abstract) (77 Refs)

10. MEASUREMENT OF O(6)-ETHYLDEOXYGUANOSINE AND N-(DEOXYGUANOSIN-8-YL)-N-ACETYL-2-AMINOFLUORENE IN DNA BY HIGH-SENSITIVE ENZYME IMMUNOASSAYS.

Van Der Laken CJ, Hagenaars AM, Hermsen G, Kriek E, Kuipers AJ, Nagel J, Scherer E, Welling M
Div. Chemical Carcinogenesis, Antoni Van Leeuwenhoek-Huis, The Netherlands Cancer Inst., 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Carcinogenesis; 3(5):569-572 1982

Antibodies raised in rabbits against the bovine serum albumin conjugates of O6-ethylguanosine and N-(guanosin-8-yl)-N-acetyl-2-aminofluorene have been used to develop a high-sensitive enzyme-linked immunosorbent assay (HS-ELISA) for the quantification of adducts in DNA modified by ethylating agents and N-acetyl-2-aminofluorene. Linear dose-response relations were obtained in the non-competitive HS-ELISA between 0.5 fmol and 50 fmol O6-ethyldeoxyguanosine per 2.8 ug DNA, and between 0.1 fmol and 20 fmol N-(deoxyguanosin-8-yl)-N-acetyl-2-aminofluorene per 0.8 ug DNA. The sensitivity of an ultrasensitive radioimmunoassay was in the same order of magnitude. Modification levels as low as 0.1 umol of adduct/mol DNA-nucleotides (1:10(7)) can be detected by each assay. (Author abstract) (21 Refs)

11. A DNA-BINDING PROTEIN FROM HELA CELLS WHICH BINDS PREFERENTIALLY TO DNA DAMAGED WITH ULTRAVIOLET LIGHT OR N-ACETOXY-N-ACETYL-2-AMINOFLUORENE.

Tsang SS
The University of British Columbia, British Columbia, Canada
Diss Abstr Int [B]; 42(12,pt1):4702-B 1982

A DNA-binding protein, PIII, was partially purified from extracts of Hela cells. PIII binds preferentially to supercoiled PM2 DNA treated with ultraviolet light (UV-DNA) or N-acetoxy-N-acetyl-2-aminofluorene (AAAF-DNA) as compared to native supercoiled PM2 DNA. The binding is noncooperative. Nicked or linear forms of PM2 DNA (damaged or untreated) are not efficient substrates for PIII, indicating a requirement of DNA supercoiling for the binding activity of PIII. The possible nature of the DNA-binding sites for PIII is discussed. PIII is a protein as indicated by its sensitivity to proteinease K. The sedimentation coefficient of the protein estimated by glycerol gradient centrifugation is 2.0-2.5 S corresponding to a molecular weight of about 20-25,000 if the protein is spherical. The binding between UV- or AAAF-DNA and PIII is optimal at around 100-200 mM NaCl and is relatively independent of temperature and pH. MgCl2 and MnCl2 at concentrations between 1 mM and 7mM do not markedly affect the binding but it is inhibited by sucrose, ATP and caffeine. The biological significance of PIII remains to be determined. It does not possess significant glycosylase, endonuclease or exonuclease activities. The dissociation equillibrium constant for the binding reaction of PIII the UV- or AAAF-induced binding sites on DNA is estimated to be 7x10-11M. The association rate constant and the dissociation rate constant are 4x106M-1 sec-1 and 3x10(-4) sec-1, respectively. There are at least 10(5) molecules of PIII per Hela cell. (no Refs)

OTHER FUSED RING AMINES

12. INHALATION CARCINOGENESIS: AN OVERVIEW.

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Recent Results Cancer Res; 82:1-10 1982

Environmental carcinogens and their site specific action under conditions of inhalation are considered. The main carcinogens to which man is currently known to be exposed, their mode of penetration, and the histological types of carcinoma they produce are listed. Carcinogens identified in tobacco smoke include dimethylnitrosamine, diethylnitrosamine, methylethylnitrosamine, N-nitrosopyrolidine, nitrosopiperidine, benzo(a)pyrene, methylbenzo(a)pyrene, dibenz(a,h)acridine, dibenz(a,j)acridine, dibenz(c)carbazole, Beta-naphthylamine, benzo(b)fluoranthene, benzo(j)fluoranthene, methylfluoranthene, benzo(a)anthracene, chrysene, methchrysenes, and benzo(c)phenanthrene. A complex aerosol like tobacco smoke is particularly oncogenic due to synergism between components, small size of particles, and the repetitive nature of the exposure. The list of chemical environmental inhaled carcinogens will undoubtedly grow. Difficulties experienced in the detection of environmental carcinogens are discussed. Mechanisms implicated in carcinogenesis at respiratory surfaces are briefly reviewed. (45 Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

13. GLYCOSAMINOGLYCANS IN 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE-INDUCED RAT HEPATIC CANCER.

Kojima J, Nakamura N, Kanatani M, Akiyama M
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Cancer Res; 42(7):2857-2860 1982

The changes in glycosaminoglycans in livers of rats with 3'-methyl-4-dimethylaminoazobenzene-induced hepatic cancer were examined and compared with those in fetal liver. The incorporation of 35S into sulfated glycosaminoglycans in hepatic cancer tissue was also studied after ip injection of Na235SO4. The major component of glycosaminoglycans in healthy adult rat liver was heparan sulfate (61.7%), with hyaluronic acid (21.1%), dermatan sulfate (13.1%), and chondroitin sulfate (4.0%) as minor components. The quantities of all of the examined glycosaminoglycans were higher in tumors than in normal liver, but chondroitin sulfate and hyaluronic acid were more prevalent in the tumors (about 51 and 7 times higher, respectively). As a result, the share of heparan sulfate was decreased (37.1%) in the tumors. The high content of chondroitin sulfate (about 30 times) and the decreased share of heparan sulfate (29.0%) were also observed in fetal liver. The incorporation of 35S into individual glycosaminoglycans varied markedly. Approx 90% of the label in glycosaminoglycans of healthy liver was found in a heparan sulfate fraction 4 hr after injection. In hepatic cancer tissue, however, 35S incorporation into both chondroitin sulfate and dermatan sulfate fractions was increased about 6.5-and 5.6-fold, respectively, of those in healthy liver. (Author abstract) (23 Refs)

14. ALPHA-FETOPROTEIN SYNTHESIS DURING EARLY STAGES OF HEPATOCARCINOGENESIS IN MICE WITH DIFFERENT SENSITIVITY TO ORTHO-AMINOAZOTOLUENE.

Serova IA, Kaledin VI, Kostyrev OA, Gruntenko EV
Inst. Cytology and Genetics, Novosibirsk, USSR
Dokl Akad Nauk SSSR; 263(5):1245-1249 1982

Alpha-fetoprotein (AFP) synthesis during ortho-aminoazotoluene (OAT) induced liver carcinogenesis was studied in OAT-sensitive DD/He, DBA/2J, CBA/LacSto, and A/He mice and in OAT-resistant CC57BR/Mv and BALB/cLacSto mice. The ip or sc administration of OAT produced marked necrotic changes in the liver of sensitive mice. Resistant mice and sensitive CBA mice did not show morphological changes in the liver tissue. Both sensitive and resistant mice showed the first peak of AFP on day 4 after OAT administration. The resistant mice showed normalization of AFP blood levels, while the sensitive mice developed the second increase of AFP level. (10 Refs) (In RUS)

15. COMPARATIVE MUTAGENICITY OF DIMETHYLAMINOAZOBENZENE AND ANALOGUES IN SALMONELLA.

Zeiger E, Pagano DA
Cellular and Genetic Toxicology Branch, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Carcinogenesis; 3(5):559-561 1982

The mutagen and hepatocarcinogen 4-dimethylaminoazobenzene (DAB) and three of its structural analogues, N-methyl-5-phenylazoindoline, 4-N-pyrrolidinylazobenzene and 4'-ethyl-4-N-pyrrolidinylazobenzene were tested for mutagenicity in Salmonella typhimurium TA1538. DAB was used as a standard and it was found that an S-9 mix containing 30% Aroclor-induced rat liver S-9 produced more mutagenic product than did an S-9 mix containing the standard 10% S-9. All chemicals tested were mutagenic and required S-9. Both pyrrolidine analogues produced similar responses to DAB, while the indoline was only weakly mutagenic. (Author abstract) (11 Refs)

16. ANTIGENIC CHANGES IN NONHISTONE PROTEINS DURING AZO DYE HEPATOCARCINOGENESIS.

Schmidt WN, Gronert BJ, Page DL, Briggs RC, Hallica LS
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 42(8):3164-3174 1982

We have investigated the appearance of specific nonhistone proteins during azo dye induced hepatocarcinogenesis in the rat. Groups of animals fed azo dye-containing diet were sacrificed at approx 3-wk intervals, portions of their livers were examined histologically, and the remaining material was fractionated into chromatin and cytoplasmic fractions. Livers of the azo dye-fed animals exhibited histological changes that have been classically attributed to the course and development of cancer; by 28 to 30 wk of treatment, nearly all animals had developed hepatomas. Heterogeneous rabbit antisera were prepared to dehistonized chromatin from several azo dye-induced hepatomas. These antisera were then used to assess various chromatins for the appearance of antigens specific for neoplasia during induced carcinogenesis using immunodetection of antigens separated electrophoretically and transferred to nitrocellulose. Changes in the immunoreactivity of liver chromosomal proteins during carcinogen treatment were evident after 3 wk, and the antigenic profiles of various chromatin samples gradually assumed the characteristics of the hepatoma. The transformation was accompanied by qualitative changes in chromosomal protein antigens, and although these antigenic species were not directly quantitated, noticeable enrichment of tumor-specific species occurred with treatment time. Immunotransfer assays of cytoplasmic fractions indicated most antigens to be specific for chromatin. Normal tissue chromatin exhibited minimal immunoreactivity, and slightly more antigenic homology was noted with regenerating liver and most transplantable tumor chromatins. Interestingly, the transplantable tumor Walker 256 carcinosarcoma was highly enriched in antigens recognized by antisera to azo dye hepatoma dehistonized chromatin. These studies establish a definite chronological correlation between the chemical induction of cancer and sequential changes in the immunological specificity of nonhistone protein antigens. (Author abstract) (56 Refs)

17. CARCINOGENESIS BIOASSAY OF C.I. ACID RED 14 (CAS NO. 3567-69-9) IN F344 RATS AND B6C3F1 MICE (FEED STUDY).

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P. O. Box 12233, Research Triangle Park, NC, 27709
Carcinogenesis Bioassay of C.I. Acid Red 14 (CAS No. 3567-69-9) in F344 Rats and B6C3F1 Mice (Feed Study). Bethesda, MD, NIH Publication No. 82-1776, (220): 147 pp., 1982.

A carcinogenesis bioassay of textile grade CI Acid Red 14 (67%-71% purity) was conducted by feeding diets containing 6,000 or 12,500 ppm of this dye for 103-104 wk to groups of 50 male F344 rats, 12,500 or 25,000 ppm to groups of 50 female F344 rats, and 3,000 or 6,000 ppm to groups of 50 B6C3F1 mice of either sex. Groups of 90 untreated rats of either sex and 50 untreated mice of either sex served as controls. Throughout the study, mean body wt of dosed rats of either sex and of dosed female mice were comparable with those of the controls, while the mean body wt of high-dose male mice was slightly lower than that of the controls. Fourteen male rats in the low-dose group and 2 in the high-dose group accidentally drowned between wk 84 and 103; 56% and 60% of these groups survived to terminal kill compared with 78% of the controls. These losses may have reduced the sensitivity of the assay in male rats. Rats and mice may have tolerated higher doses, but the slight depression of mean body wt in high-dose male mice and the non-neoplastic lesions observed in dosed female mice and in rats of both sexes suggest that doses administered in this study could be considered max tolerated doses. Endometrial stromal polyps of the uterus were observed in high-dose female rats at an incidence significantly higher ($p = 0.008$) than that seen in the controls (controls: 9/87, 10%; low-dose: 11/50, 22%; high-dose: 14/50, 28%). However, the observed incidence of this tumor in the dosed groups was similar to the historical rate in untreated female F344 rats at this laboratory (65/286, 23%; range 10%-37%). Hence, the increased incidence of this lesion is not regarded as being associated with the administration of CI Acid Red 14. Administration of CI Acid Red 14 to mice was not associated with an increased incidence of any tumor type. Under the conditions of this bioassay, CI Acid Red 14 was not carcinogenic for F344 rats or B6C3F1 mice of either sex. (Author abstract) (10 Refs)

HETEROCYCLIC AMINES

18. INTERCALATING SUBSTANCES DO NOT INDUCE SISTER-CHROMATID EXCHANGES (SCES) IN VIVO.

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Mutat Res; 104(4/5):261-266 1982

Acridine derivative, proflavine (PF), and phenothiazine derivatives, methylene blue (MB) and chlorpromazine (CPZ) were investigated in vivo (Chinese hamsters, 6-12 mo old) in the sister-chromatid exchange (SCE) test for the demonstration of a possible DNA-damaging effect. To evaluate the cellular proliferation, the distribution of metaphases of the first, second, and third generations were determined in 200 mitoses each. Cells that had replicated their DNA exclusively before the implantation of 5-bromodeoxyuridine could not be distinguished from the first metaphases, and cells that had gone through more than three cell cycles were counted as third mitoses. PF as well as MB and CPZ did not lead to a significant induction of SCE in the bone marrow of Chinese hamster. CPZ was tested up to a concentration corresponding to 4x the therapeutic dose in man. PF and MB were tested in vivo up to the same concentration level without showing any effect. An increase of the dose was limited by the solubility of the substances. The distribution of the first, second, and third mitoses showed that the proliferation of the cells analyzed in the bone marrow was not delayed [illegible] comparison with the control. To exclude artifacts from the experimental procedure, cyclophosphamide (CP) was tested as a positive control. CP led to a pronounced increase in the SCE frequencies without impending the proliferation of the cells. (13 Refs)

19. DNA-REPAIR DEFICIENCIES DO NOT AFFECT INTERCALATOR-INDUCED CYTOTOXICITY OR DNA SCISSION IN HUMAN CELLS.

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Building 37, Room 5D17, 9000 Rockville Pike, Bethesda, MD, 20205
Mutat Res; 104(4/5):295-304 1982

Toxicity of the DNA intercalator 4'-(acridinylamino)-methanesulfon-m-aniside (m-AMSA) was compared to the toxicity of xeroderma pigmentosum (XP) and ataxia telangiectasia (A-T) cells, and normal human fibroblasts and the protein associated DNA-strand breaks produced by m-AMSA are discussed. The efficiency of m-AMSA in reducing colony-forming ability was the same in all three human fibroblast lines. Quantification of m-AMSA production of DNA-strand breaks by alkaline elution also revealed no differences among the three lines. Results differed from those of experiments which measured cytotoxic effect and DNA-strand breaks produced by damaging agents. Scission produced by m-AMSA also disappeared similarly in normal, XP, and A-T lines. The m-AMSA breaks in all three cell lines were associated with comparable magnitudes of DNA-protein crosslinking. The concentration of m-AMSA associated with each cell type was measured by the use of radioactive compound. The normal cells displayed no reduction in either m-AMSA sensitivity or single-strand break production. A true increased sensitivity of the variant cells thus was not masked by deficient m-AMSA uptake. The effects upon DNA biochemistry and cell survival produced by m-AMSA appeared to be mediated by cellular factors other than those that are deficient in human cell lines abnormally sensitive to other DNA-reactive agents. (31 Refs)

20. STUDIES OF THE MODE OF ACTION OF ANTITUMOR TRIAZENES AND TRIAZINES - IV. THE METABOLISM OF 1-(4-ACETYLPHENYL)-3,3-DIMETHYLTRIAZENE.

Farina P, Gescher A, Hickman JA, Horton JK, D'Incalci M, Ross D, Stevens MF, Torti L
(c/o Hickman) Dept. Pharmacy, Univ. Aston in Birmingham, Birmingham B4 7ET, England
Biochem Pharmacol; 31(10):1887-1892 1982

The metabolism of 1-(4-acetylphenyl)-3,3-dimethyltriazene has been studied in vivo and in vitro in mice. This dimethyltriazene was extensively metabolized in vivo and HPLC analysis of the plasma revealed the presence of two metabolites, the monomethyltriazene, 1-(4-acetylphenyl)-3-methyltriazene, and the arylamine, 4-aminoacetophenone. The dimethyltriazene was also biotransformed in vitro by a 9,000 g fraction of mouse liver homogenate to products which were selectively toxic to TLX5 lymphoma cells. HPLC analysis of the products of in vitro metabolism under these conditions showed the presence of the monomethyltriazene but in an amount insufficient to account for the observed cytotoxicity. The monomethyltriazene was itself rapidly biotransformed by a 9,000 g fraction of mouse liver homogenate, and by isolated mouse hepatocytes. (Author abstract) (11 Refs)

21. EFFECT OF PRAZIQUANTEL, A NEW ANTISCHISTOSOMAL DRUG, ON THE MUTATION AND TRANSFORMATION OF MAMMALIAN CELLS.

Billings PC, Heidelberger C
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Cancer Res; 42(7):2692-2696 1982

Praziquantel (PQ), a tetrahydroquinoline derivative, is a new clinically effective antischistosomal drug, which has been shown to lack or to possess very weak mutagenic activity. However, in bacteria, this compound can act as a weak comutagen that increases the mutagenicity of several chemical mutagens and carcinogens. We have found that PQ can act as a very weak comutagen in animal cells. At 10 to 50 ug/ml, PQ increased the mutagenicity of N-methyl-N'-nitro-N-nitrosoguanidine and 2-methoxy-6-chloro-9-[3-(2 chloroethyl)aminopropylamino]acridine dihydrochloride about two-fold in Chinese hamster V-79 cells. In C3H/10T1/2 mouse embryo cells, PQ exhibited only negligible comutagenic activity. PQ did not oncogenically transform C3H/10T1/2 cells but had a pronounced effect on 3-methylcholanthrene-induced transformation of these cells. When PQ was coadministered with or added after 3-methylcholanthrene treatment, the number of Type III foci produced was about five-fold lower than in cultures treated with 3-methylcholanthrene alone. Therefore, PQ can inhibit Type III focus formation in C3H/10T1/2 cells. (Author abstract) (16 Refs)

22. TWO POPULATIONS OF CELLS WITH DIFFERING PROLIFERATIVE CAPACITIES IN ATYPICAL ACINAR CELL FOCI INDUCED BY 4-HYDROXYAMINOQUINOLINE-1-OXIDE IN THE RAT PANCREAS.

Rao MS, Upton MP, Subbarao V, Scarpelli DG
Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611
Lab Invest; 46(5):527-534 1982

A single intravenous injection of 4-hydroxyaminoquinoline-1-oxide in male Wistar rats at a dose of 6 mg per kg of body weight induced atypical acinar cell foci in 100% of the animals. Atypical acinar cell foci could be classified histologically as basophilic and acidophilic foci and acidophilic nodules. Cells in basophilic foci were large, contained an irregular nucleus and a markedly basophilic cytoplasm with a few to small number of zymogen granules (zymogen-poor cells). By transmission electron microscopy, these cells showed markedly irregular plasma membranes, a well-developed rough endoplasmic reticulum and a few zymogen granules. Cells in acidophilic foci and nodules contained an intensely eosinophilic granular cytoplasm (zymogen-rich cells) and a large oval to round nucleus. By transmission electron microscopy, the cells showed zymogen-rich cytoplasm and irregular lateral plasma membranes. Mitotic activity was completely absent or very rarely observed in normal pancreas or basophilic foci, in contrast to acidophilic foci and nodules in which a mean value of 2.75 +-1.27 per 1,000 cells was found. Autoradiography confirmed these differences between the proliferative capacity of cells in basophilic foci (1 +-1 labeled nuclei per 1,000 cells) and acidophilic foci (23.2 +-3.15 labeled nuclei per 1,000 cells). These studies indicate that 4-hydroxyaminoquinoline-1-oxide induces two types of atypical acinar cell foci with different morphologic features and proliferative capacity. (Author abstract) (35 Refs)

23. HYPERSENSITIVITY OF ATAXIA TELANGIECTASIA SKIN FIBROBLASTS TO DNA ALKYLATING AGENTS.

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Mutat Res; 94(2):369-382 1982

Three ataxia telangiectasia (AT) skin fibroblasts cells strains, AT4BI, AT5BI, and AT2BE (CRL 1343) were studied for survival following treatment with methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitroquinoline-1-oxide (4NQO) and results were compared to those obtained from three normal human fibroblast cell strains. None of the AT fibroblast strains were significantly more sensitive to MNNG treatment than the av normal survival. Similarly, no significant difference was observed in D10 values among the AT fibroblast strains and the normal av D10 value. Strain AT5BI appeared to be moderately sensitive to MMS treatment compared to the normal av survival. Comparison of the D0 value for strain AT5BI, 0.29 milliM (mM) vs the normal av of 0.38 +-0.03 mM indicated a significant difference in the slope of the survival curve between strain AT5BI and the normal av survival curve. Strain AT4BI was hypersensitive to MMS treatment only when D0S were compared. All three fibroblast strains were significantly more sensitive to treatment with EMS than the normal controls. AT4BI, AT5BI, and AT2BE had D10S of 16, 13, and 15 mM, respectively, vs the normal human fibroblast av D10 value of 28 mM. AT4BI and AT2BE were abnormally sensitive to treatment with 4NQO as compared to the survival of the normal human fibroblast strains. (61 Refs)

REVIEWS AND OTHER RELATED STUDIES

24. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H
Lab. Government Chemist, London, England
IARC Sci Publ (40): 347 pp., 1981.

Analysis of industrial and non-industrial aromatic amines (AA) and azo dyes (AD) is reviewed. AA and AD are considered with respect to biological activity (carcinogencity of AA and AD and their role in the development of human cancer, metabolic activation of AD), occurrence and monitoring in industry (biological monitoring of AA and their metabolites using short-term tests for carcinogenicity, AA of major industrial importance, survey of technics for estimating and monitoring AA of major industrial importance), AA and dyes in non-industrial exposures (mutagenic heterocyclic amines in cooked food; survey of the analysis of 2-acetylaminofluorene; overview of the toxicity, metabolism, and analysis of phenacetin; food colors), methods of analysis for AA and dyes in foods (analysis of 2-acetylaminofluorene in animal feed by spectrophotofluorescence, identification of water-soluble colors in food using paper and thin-layer chromatography, extraction of water-soluble colors from food using polyamide columns). (667 Refs)

25. MUTAGENS PRODUCED BY THE PYROLYSIS OF OPIUM AND ITS ALKALOIDS AS POSSIBLE RISK FACTORS IN CANCER OF THE BLADDER AND OESOPHAGUS.

Malaveille C, Friesen M, Camus AM, Garren L, Hautefeuille A, Bereziat JC, Ghadirian P, Day NE, Bartsch H

(c/o Bartsch) Div. Environmental Carcinogenesis, International Agency Res. on Cancer, 150 cours Albert-Thomas, 69372 Lyon, Cedex 8, France

Carcinogenesis; 3(5):577-585 1982

Samples of opium pipe scrapings (opium dross, called sukhteh locally), but not of crude opium, collected in an area with a high incidence of esophageal cancer in north-east Iran, were shown to contain pro-mutagens, producing mostly frameshift mutations in Salmonella typhimurium strains TA1538 and TA98 after metabolic activation. Pyrolysis of opium and of its major alkaloid, morphine, yielded smoke condensates with mutagenic activities 10 and 100x higher, respectively, than that of the sukhteh samples tested. Heterocyclic aromatic hydrocarbons and primary aromatic amines present at different concentrations in these three pyrolysates are considered to be the major active principles. Opium addiction has been implicated as a risk factor in bladder cancer in humans and the ingestion of opium pyrolysates, in conjunction with dietary deficiencies, may be related to the high incidence of esophageal cancer in north-east Iran, although causality has not been established. (Author abstract) (29 Refs)

26. MUTAGENIC RESPONSES OF FIVE INDEPENDENT GENETIC LOCI IN CHO CELLS TO A VARIETY OF MUTAGENS. DEVELOPMENT AND CHARACTERISTICS OF A MUTAGEN SCREENING SYSTEM BASED ON SELECTION FOR MULTIPLE DRUG-RESISTANT MARKERS.

Gupta RS, Singh B
Dept. Biochemistry, McMaster Univ., Hamilton L8N 3Z5, Canada
Mutat Res; 94(2):449-466 1982

Response of several well characterized genetic markers such as those involving resistance to thioguanine, emetine, ouabain, 5-6-dichlororibofuranosylbenzimidazole, and methylglyoxal bisguanylhydrazone towards a number of direct- and indirect-acting mutagens was assessed in proline-requiring Chinese hamster ovary (CHO) cell line. Direct-acting alkylating and DNA-adduct forming agents such as beta-propiolactone, ethyleneimine, N-nitrosomethylurea, 4-nitroquinoline-N-oxide, methyl methanesulfonate, and ethyl methanesulfonate; DNA intercalating and cross-linking agents such as ICR-170, acridine orange, ethidium bromide, mitomycin C, and actinomycin D; and chemicals requiring microsomal activation in other systems such as benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, benzidine, and beta-naphthylamine were examined. The response of various agents was determined at only two or three concentrations which should have resulted in between 10-80% cell killing. Mutation frequencies of different genetic markers which were observed in the control and mutagen-treated cultures, as well as the mutagenesis significance ratio of various markers, which provide a measure of their relative mutagenic response are shown. Of the genetic loci, no one single locus showed higher response to all of the chemicals, instead, depending upon the chemical, specific loci were found to be more responsive than others. Results indicated that CHO cells possess significant capacity for the metabolic activation of many procarcinogens, and also underscore the merits of measuring the mutagenic response at multiple genetic loci in mutagen screening studies. (40 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.
Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.
Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
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4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.
Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.
Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982
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6. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.
Bishun NP
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J Surg Oncol; 20(2):115-118 1982

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Raithel HJ, Schaller KH
Institut fur Arbeits- und Sozialmedizin, Poliklinik fur Berufskrankheiten, Universitat Erlangen-Nurnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany
Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981
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8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.
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10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.
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Am J Public Health; 72(6):585-588 1982

11. RISK OF RADIOLOGICAL EXAMINATIONS.
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Pol Przegl Radiol; 45(6):383-386 1981
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12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)
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IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

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Proc Soc Exp Biol Med; 170(2):115-125 1982

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DIETARY FACTORS IN CARCINOGENESIS

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Maganova NB
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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

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24. TRENDS IN THE INCIDENCE OF GASTRIC CARCINOMA (MEETING ABSTRACT)
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Occupational Exposures to Uranium: Processes, Hazards, and Regulations. Available from National Technical Information Service, Springfield, VA, as PNL-3341-USUR-01:, 91 pp., 1981.

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Trosko JE, Chang CC
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Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Adv Exp Med Biol; 136(partA):809-820 1982

41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

Hepatogastroenterology; 28(4):221-228 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Homma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

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45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

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Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

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46. TRANSLATION OF PHARMACOKINETIC/BIOCHEMICAL DATA INTO RISK ASSESSMENT.

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Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

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Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

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SERIES CK10 No. 82/12

DECEMBER, 1982

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ANILINES AND EXTENDED ANILINES

1. DISPOSITION AND METABOLISM OF THE CARCINOGEN REDUCED MICHLER'S KETONE IN RATS.

McCarthy DJ, Struck RF, Shih TW, Suling WJ, Hill DL, Enke SE
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Cancer Res; 42(9):3475-3479 1982

Studies on the in vivo and in vitro disposition of 4,4'-[14C]methylenebis(N,N-dimethyl)benzamine (reduced Michler's ketone, RMK) were performed. Osborne-Mendel rats retained, after 24 hr, 78% of a po dose of [14C]RMK. At 24 hr after an ip dose, fat, liver, and intestine represented major sites for deposition of radioactivity. The major urinary metabolite of RMK, representing 36% of the total radioactivity recovered in the urine was N,N'-diacetyl-4,4'-(hydroxymethylene)dianiline. In vitro microsomal metabolism of RMK involved demethylation. Products included N,N-dimethyl-4,4'-methylenedianiline, N,N'-dimethyl-4,4'-methylenedianiline, N-methyl-4,4'-methylenedianiline, and 4,4'-methylenedianiline, representing 44.7, 5.3, 11.8, and 6.9%, respectively, of the total radioactivity recovered from the reaction mixture. Although none of the microsomal

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metabolites was a direct-acting mutagen in the standard Salmonella typhimurium assay, all could be activated to mutagens when incubated with 9,000 x g liver supernatants and reduced nicotinamide adenine dinucleotide phosphate. The activation of 4,4'-methylenedianiline to a mutagen suggests that the methyl groups of RMK are not required for the conversion of RMK to a reactive electrophile. (Author abstract) (15 Refs)

2. DISTRIBUTION, ELIMINATION, AND TEST FOR CARCINOGENICITY OF 2,4-DINITROTOLUENE IN STRAIN A MICE.

Schut HA, Loeb TR, Stoner GD
Dept. Pathology, Medical Coll. Ohio, Toledo, OH, 43699
Toxicol Appl Pharmacol; 64(2):213-220 1982

The carcinogenicity of 2,4-dinitrotoluene (2,4-DNT) was reevaluated in terms of its ability to induce lung adenomas in strain A mice; tissue distribution and elimination were also studied following total ip doses of 600, 1,500, or 3,000 mg/kg of radiolabeled 2,4-DNT. The av number of lung tumors per mouse was not significantly different from that in vehicle-treated or untreated controls. After administration of 1, 10, or 100 mg/kg 2,4-DNT, excretion in urine was rapid, especially during the first hr, with 52.5, 60.1 and 67/0%, respectively, being eliminated within 4 hr. Early uptake in the large intestine was slight; blood concentration decreased with time, especially during the first hr after administration. At times earlier than 2 hr, levels in the liver were 2-to 4-fold higher than in the blood, whereas after 2 hr, the two compartments had comparable concentrations. A similar situation existed with respect to the kidney, except that higher levels than in the blood persisted up to 3 hr after administration. Elimination of radioactive material from the lungs ranged from 0.05-0.2% of the administered dose. Adipose tissue took up maximal levels amounting to 3.9-4.7% of the administered dose, whereas levels of 2,4-DNT in the brain, heart, and spleen were barely detectable and did not change with time and dose. The liver and small intestine seem to be the major sites of 2,4-DNT metabolism, which is virtually complete in these organs at 1 hr after ip administration. (23 Refs)

3. THE INFLUENCE OF SEX, DOSE, TIME, AND CROSS ON NEOPLASIA IN MICE GIVEN BENZIDINE DIHYDROCHLORIDE.

Nelson CJ, Baetcke KP, Frith CH, Kodell RL, Schieferstein G
Dept. Health and Human Services, Food and Drug Admin, Natl. Center for Toxicological Res., Jefferson, AR, 72079
Toxicol Appl Pharmacol; 64(2):171-186 1982

Features of liver tumor development associated with exposure of mice to benzidine dihydrochloride (0, 30, 60, 120, 200, and 400 ppm in water) were studied. Half the mice (1,728) were obtained from mating C57BL/6JfC3Hf/Nctr females with BALB/cStCrLfC3Hf/Nctr males, and were called F-1 hybrids; another 1,728 mice were obtained by mating an F-1 hybrid inter se, and were called the monohybrid cross. Animal weight, water consumption, hepatic foci of cellular alterations and liver tumors, liver tumor dose-response relationship, survival time, time-to-tumor analysis, and other variables were monitored, usually at 40, 60, and 80 wk. Monohybrid males were more susceptible than F-1 hybrid males to the toxic effects of benzidine dihydrochloride as exhibited by weight loss. Monohybrid males also experienced considerable early mortality of unknown cause. F-1 and monohybrid animals were very similar for a number of dose-response relationships, including hepatic foci of cellular alterations, liver tumor incidence, liver tumor survival, and overall survival. There was a slight difference in liver tumor survival between F-1 and monohybrid females. Positive relationships between certain hepatic foci of cellular alterations and hepatocellular adenomas were suggested by the results for females, but not for males. The time required for death from liver tumors after initial tumor formation was not dependent on either sex or dose level of benzidine. The predominant benzidine-related cause of death was liver tumors, although females may have been affected by other unknown toxic factors. (28 Refs)

4. LIGHT INDUCES MUTAGENICITY OF HAIR-DYE P-PHENYLENEDIAMINE.

Nishi K, Nishioka H
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 104(6):347-350 1982

Mutagenicity of p-phenylene-diamine (PPD), a main constituent in hair dyes, in the Ames Salmonella/microsome test in the dark was insignificant, while exposure to light in TA98 with S9 mix, increased mutagenicity considerably. Mutagenicity reached a max (approx 2,000 revertant colonies per plate) after illumination for 60 min. Silica-gel thin-layer chromatography of light-exposed PPD suggested that the photochemical product may be the trimer Bandrowski's base. (10 Refs)

5. 3-AMINOBENZAMIDE SYNERGISTICALLY INCREASES SISTER-CHROMATID EXCHANGES IN CELLS EXPOSED TO METHYL METHANESULFONATE BUT NOT TO ULTRAVIOLET LIGHT.

Morgan WF, Cleaver JE
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, San Francisco, CA, 94143
Mutat Res; 104(6):361-366 1982

The effects of 3-aminobenzamide on the production of sister-chromatid exchanges induced by methyl-methanesulfonate (MMS) and UV light in Chinese hamster ovary cells (CHO) and Simian virus 40 (SV40)-transformed human cells (GM637) were investigated. Synergism between 3-aminobenzamide and MMS was observed, while no significant effect was seen with 3-aminobenzamide and UV light in either cell type. (25 Refs)

6. DISPOSITION OF 3,3'-DICHLOROBENZIDINE IN THE RAT.

Hsu RS, Sikka HC
Great Lakes Res. Lab., State Univ. New York, Coll. at Buffalo, 1300 Elmwood Ave., Buffalo, NY, 14222
Toxicol Appl Pharmacol; 64(2):306-316 1982

Absorption, excretion, tissue distribution, and metabolism of 3,3'-dichlorobenzidine (DCB) were determined in male rats following po administration. The concentration of [14C]DCB-derived radioactivity and the parent compound in plasma of rats following po dose of 40 mg/kg reached a peak 8 hr after dosing, and declined thereafter in a biphasic manner than could be described by a two-compartment open model with first-order absorption. Following a single po dose of 6.4 or 40 mg [14C]DCB/kg, highest concentrations after 24 hr were found in the liver, followed by kidney, lung, spleen, heart, pancreas, and testes. On a percentage of total dose basis, the liver, kidney, lung, and muscle retained the most unexcreted radioactivity 96 hr after a 40 mg/kg dose. Multiple po doses of 6 mg/kg/day for 6 days resulted in tissue levels 24 hr after the last dose which were approx 3-4x higher than in animals that received a single dose. Animals receiving a single oral dose of 40 mg/kg DCB excreted over 90% of the administered radioactivity via the urine and feces by 72 hr (64.9 and 27.7%, respectively). Bile duct-cannulated rats accumulated 65% of administered radioactivity in the bile at 24 hr, whereas in bile duct-ligated rats 75% of radioactivity appeared in the urine in 96 hr, with less than 1% in the feces, indicating that biliary excretion is the only process of elimination into the gastrointestinal tract. Analysis of liver and bile products indicated that urine contained a high percentage of unconjugated material, whereas conjugated metabolites predominated in bile. Chromatography revealed at least five metabolites besides DCB in urine and bile, and showed that only 9-16% of DCB remained unmetabolized 24 hr after po administration of 40 mg/kg. (23 Refs)

7. IN VITRO CARCINOGENESIS IN CANINE BLADDER (MEETING ABSTRACT).

Klaunig JE, Constantini MG, Barut BA, Goldblatt PJ
Department of Pathology, Medical College of Ohio, Toledo, OH
Lab Invest; 46(1):45A 1982

As part of our overall investigation of mechanisms of bladder carcinogenesis, we have developed methods for establishing primary and secondary cultures of canine bladder urothelial cells. Urinary bladder from adult dogs of mixed breed were removed immediately after exanguination. Four pieces of bladder were placed urothelium side up per 60-mm cultured dish. Two milliliters of Ham's 151 culture medium were added per dish, and dishes were maintained at 36.5 C in a humidified CO2 incubator. Epithelial cells were seen extending from the explants 2 to 3 days after culture initiation. Within 2 to 3 weeks cells were almost confluent on the culture dish. The inclusion of fetal bovine serum in the medium resulted in the overgrowth of epithelial cultures by fibroblasts. The calcium concentration in the medium had a significant influence on differentiation and growth of primary urothelial cells. A concentration of 1 x 10(-4) M calcium appeared optimal for cell growth and prevention of differentiation. Secondary cultures were initiated by trypsinization of primary cultures. Fetal bovine serum was required in the medium for secondary culture cell growth. DNA repair evident in explants, primary, and secondary cultures following exposure to methylnitrosourea aflatoxin B1 4-aminobiphenyl, and benzo(a)pyrene. UDS (unscheduled DNA synthesis) in each compound displayed a linear dose response. Radiolabeled benzo(a)pyrene was metabolized and covalently bound to DNA in bladder explants, primary and secondary cultures. (no Refs)

8. THE COMPARATIVE TOXICITIES AND CARCINOGENICITIES OF BENZIDINE AND DIRECT BLUE 6 IN RATS (MEETING ABSTRACT).

Mennear JH, Gupta BN
National Toxicology Program, National Institute of Environmental Health Services, Research Triangle Park, NC, 27709
Toxicologist; 2(1):35 1982

Direct Blue 6, a bisazobiphenyl dye known to be metabolized to benzidine (B) produces hepatocellular carcinoma when fed to rats at dietary concentrations of 1500 and 3000 ppm. The rapid onset of carcinoma (4 weeks) suggested that the effect might be mediated through mechanisms other than simple metabolism to B. The objective of the present study was to compare the potencies of the dye and B with respect to general toxicity and carcinogenicity. Groups of 20 female F344 rats were exposed to drinking water containing either B-2HCl (100-400 ppm) or the dye (500-2000 ppm) for up to 90 days. The concentrations of B were selected to be equivalent to B exposure if dye-treated rats completely metabolized the chemical. Based on water consumption, the average daily doses of B were 10, 21, 28, 31 mg/kg while the B equivalents of the dye consumptions were 13, 22, 30 and 37 mg/kg/day. All rats exposed to the two highest doses of B died within 9 weeks while only 6 rats exposed to the high dye concentration died during the study. Among rats surviving to terminal sacrifice, both chemicals produced dose-related increases in serum gamma glutamyl transpeptidase with the magnitude of effect produced by the 21 mg/kg/day dose of B being similar to that produced by the highest dose of the dye. Additional dose-related effects produced by both chemicals included: thymic involution, increased liver weights, and grossly observable hepatic nodules. Hepatocellular carcinoma was diagnosed in some rats that died after receiving 28 mg/kg/day of B for up to 9 weeks. (no Refs)

9. A COMPARISON OF CARCINOGEN INDUCED OVAL CELL PROLIFERATION AND CHEMICALLY INDUCED BILE DUCT PROLIFERATION IN RAT LIVER (MEETING ABSTRACT).

Sell S
University of California, San Diego, La Jolla, CA, 92093
Fed Proc; 41(3):378 1982

' Oval' cells which appear in the livers of rats exposed to chemical hepatocarcinogens are believed to be of bile duct origin. In order to study this, alphafetoprotein (AFP) production and morphologic changes in the livers of rats fed 0.05% N-2-fluorenylacetamide in a choline devoid diet (CD-FAA) were compared to those induced by feeding 0.15% 4,4'diaminodiphenylmethane (DDPM). Following a two-week feeding of CD-FAA, proliferation of 'oval' cells begins in the portal area and extends rapidly across the liver lobule. Bile duct-like structures are found throughout the liver lobule as a late component of oval cell proliferation. Associated with these changes is a rapid and high elevation of serum AFP and many of the oval cells and duct-like structures contain AFP and albumin when examined by immunofluorescence. Normal bile ducts do not contain AFP or albumin. In contrast, DDPM produces a progressive proliferation of bile ducts, extending from the portal area into the adjacent liver lobule. This is not associated with AFP elevation in the serum and the newly formed ducts do not contain AFP or albumin. It is concluded that the duct-like structures seen as a component of oval cell proliferation do not necessarily represent differentiation of oval cells into bile ducts. Oval cells may have a stem-like capacity to form cell types not seen in the normal adult or fetal liver. (no Refs)

10. STUDIES ON THE METABOLIC ACTIVATION OF BENZIDINE BY ISOLATED RAT HEPATOCYTES.

Brouns RM, Bos RP, Van Doorn R, Henderson PT
Inst. Pharmacology and Toxicology, Univ. Nijmegen, Nijmegen, The Netherlands
Toxicology; 23(2/3):235-247 1982

Isolated parenchymal liver cells of adult male Wistar rats were exposed to benzidine and the mutagenic activity of the resulting metabolite in the Ames Salmonella typhimurium assay was determined. Induction of DNA repair in the liver cells themselves was also studied. Intact rat liver cells metabolized the benzidine to more mutagenic derivatives than did the 9,000-g supernatant from the hepatocytes. Harmine (an inhibitor of N-acetyltransferase), markedly reduced the mutagenicity of derivatives produced, whereas, salicylamide (an inhibitor of sulfotransferase), had no influence. A time-dependent enhancement of mutagenicity in the Ames assay was observed when benzidine was pre-incubated with intact rat liver cells before being exposed to the 9,000 g supernatant; revertant colonies attained levels 4x those observed when only untreated supernatant was used. Exposure of liver cells to benzidine resulted in a concentration-dependent increase in 3H-thymidine incorporation up to approx 10(-5) M benzidine. Decreasing the N-acetylation and sulfation capacity of the liver cells with harmine and salicylamide, respectively, decreased the incorporation of 3H-thymidine to the level observed in the absence of benzidine, suggesting that both reactions are involved in the generation of reactive metabolites in the liver cell. Evidence was found for an N-acylated metabolite that, when activated by the 9,000 g supernatant, was considerably more mutagenic than benzidine itself. A tentative reaction scheme is presented. (22 Refs)

11. DISTRIBUTION, ELIMINATION, METABOLISM AND TEST FOR CARCINOGENICITY OF DINITROTOLUENES IN STRAIN A MICE (MEETING ABSTRACT).

Schut HA, Loeb TR, Stoner GD
Department of Pathology, Medical College of Ohio, Toledo, OH, 43699
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

The lung tumor response in strain A mice has been used extensively as an in vivo carcinogenesis bioassay. A number of dinitrotoluenes (DNT's) were tested for tumorigenic potential in this system. In the standard bioassay, 2,4-dinitrotoluene, 2,6-dinitrotoluene, 3,4-dinitrotoluene and 3.5-dinitrotoluene did not increase the frequency of lung tumors while the positive carcinogen, urethane, produced the expected increase. When administered ip at 1, 10 or 100 mg/kg, both 2,4-DNT and 2,6-DNT were excreted rapidly into the urine with greater than 50% of the dose eliminated within 1 hr and greater than 70% within 4 hr. Distribution studies in various tissues showed no evidence for preferential uptake or retention of either, 2,4-DNT or 2,6-DNT, at any of the doses tested. Both 2,4-DNT and 2,6-DNT were rapidly and extensively metabolized as evidence by the very small amounts of the injected material that could be reisolated from urine, liver and small intestine. Much larger amounts of unchanged 2,4-DNT and 2,6-DNT could be reisolated from blood and lungs and in almost all cases the extent of metabolism was similar in these two tissues. It is concluded that 2,4-DNT, 2,6-DNT, 3,4-DNT and 3,5-DNT are not carcinogenic in the strain A mouse lung tumor bioassay and that, after ip administration, both 2,4-DNT and 2,6-DNT are rapidly eliminated in the urine. In the mouse, the liver and small intestine appear to be major sites of metabolism of DNT compounds. (no Refs)

12. COMPARATIVE CARCINOGENICITIES AND TOXICITIES OF N-HYDROXY-N-ACYL-4-AMINOSTILBENES (MEETING ABSTRACT).

Hirose M, Shirai T, Lee MS, King CM
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:232 1982

The abilities of the N-hydroxy-N-formyl-4-aminostilbene (N-OH-FAS), N-hydroxy-N-acetyl-4-aminostilbene (N-OH-AAS), and N-hydroxy-N-propionyl-4-aminostilbene (N-OH-PAS) derivatives of N-hydroxy-N-acyl-4-aminostilbene to induce tumors and unschedule DNA synthesis (UDS) were determined in efforts to relate the metabolic activation of arylhydroxamic acids to their production of adverse biological effects. Hepatocytes obtained from male CD rats were allowed to attach to cover slips for 18 hr prior to treatment with the above compounds (0.1 uM to 1 mM) for 2 hr in the presence of [3H]TdR in serum-free media. On autoradiography of cells treated with N-OH-PAS, the maximum number of grains over the nuclei (36) occurred at a concentration (1 uM) 2 logs lower than with N-OH-FAS or N-OH-AAS. Control cells averaged only 1 grain per nucleus. Groups of 30 male CD rats (100 g) were given intraperitoneal injections of the agents (10 umol/kg bw) in DMSO:trioctanoin twice weekly for 6 weeks. The experiment was terminated 62 weeks after the first injection. The livers of N-OH-PAS-treated animals, at sacrifice, were larger than those of the other groups. Grossly, the number of tumor-bearing rats was 10/29 (N-OH-FAS), 18/29 (N-OH-AAS), 24/28 (N-OH-PAS), and 3/30 (solvent-treated). The number of rats with ear duct tumors were 0, 10, 13, 1; those with pancreatic tumors were 3, 7, 9, 0; and those with liver tumors were 0, 3, 6, 1, in groups given N-OH-FAS, N-OH-AAS, N-OH-PAS or solvent, respectively. (no Refs)

13. BREAST TUMORS INDUCED BY N-NITROSOMETHYLUREA (NMU) OR DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN CASTRATED MALES: ROLE OF HIGH FAT DIET (MEETING ABSTRACT).

Rivenson A, Silverman J, Weisburger J
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:275 1982

We attempted to extend the findings of Fingerhut and Veenema on the induction of prostate cancer in gonadectomized male Fischer F-344 rats on 20% and 5% fat diets, utilizing iv dosing with 7,12-dimethylbenz(a)anthracene (DMBA), and also 2',3-dimethyl-4-aminobiphenyl (DMAB), and N-nitrosomethylurea (NMU). No prostate cancers were found in rats held for 68 weeks. However, with NMU and DMAB these gonadectomized male rats had breast cancers in a higher incidence on the 20% fat diet with NMU but not with DMAB. All neoplasms were malignant, with invasion and destruction of neighboring tissues, and presenting histologically mixed glandular and squamous structures, quite distinct from lesions usually seen in females. Similar type of adeno-squamous carcinomas could be seen in tumors of the ear duct (Zymbal glands) and bulbo urethral glands developed in rats given the above carcinogens. The topographic location of the tumors labeled grossly as 'breast tumors' excluded other possible similar glandular structures and also a sweat gland tumor since the rat skin does not contain sweat glands. Other tumors noted after the carcinogens given iv were: bladder, DMAB only; small intestine and colon, NMU and DMAB; lung, DMBA, NMU, and DMAB; sc sarcoma, NMU and DMAB; stomach NMU. Several of these cancers exhibited metastases. None of the tumors noted above were present in controls. In summary, NMU and DMAB induced tumors in a number of sites, but selectively caused mammary gland adenocarcinoma and adenosquamous carcinoma, and Zymbal gland adenoepidermoid carcinoma. (1 Ref)

14. METABOLIC PATHWAYS FOR THE CARCINOGEN, BENZIDINE, WHICH RESULT IN COVALENT BINDING TO DNA (MEETING ABSTRACT).

Frederick CB, Martin CN, Weis CC, Kadlubar FF
The National Center for Toxicological Research, Jefferson, AR, 72709
Proc Am Assoc Cancer Res; 23:322 1982

Benzidine (BZ), a urinary bladder carcinogen in humans and dogs, induces hepatic tumors in mice and rats. In recent studies, we identified a single carcinogen-DNA adduct, N-(deoxyguanosin-8-yl)-N'-acetyl-BZ, in mouse and rat liver following an ip dose of BZ or N-acetylbenzidine (N-ABZ). N,N'-Diacetylbenzidine (DABZ) did not produce a detectable level of DNA binding. To determine which metabolic activation pathways result in DNA binding in vivo, we examined the N-acetylation, N-hydroxylation, N-deacetylation, and O-esterfication of BZ and its derivatives in vitro using rat liver subcellular fractions. N-ABZ, a known metabolite of BZ, was preferentially oxidized on the amide nitrogen by NADPH-fortified microsomes to yield N-hydroxy-N-ABZ. N'-Hydroxy-N-ABZ was not detected. N-Hydroxy-N-ABZ was then N-acetylated by liver cytosol and acetyl CoA to give N-hydroxy-DABZ. N-Hydroxy-DABZ was further selectively deacetylated by hepatic microsomes to yield N'-hydroxy-N-ABZ. Both of these were substrates for purified hepatic N,O-acyl-transferase, resulting in intra- and intermolecular acyl transfer, respectively, and subsequent covalent binding to added DNA. Enzymatic hydrolysis of the DNA and high pressure liquid chromatography yielded the identical C-8-deoxy-guanosine adduct found in vivo. Similar results, albeit at lower levels of binding, were obtained by reaction of N'-hydroxy-N-ABZ directly with DNA. Thus, these data suggest that N'-hydroxy-N-ABZ and N-hydroxy-DABZ are proximate carcinogenic metabolites of BZ in the rat. (no Refs)

15. COMPARISON OF N-HYDROXY-PHENACETIN (N-OH-P) AND N-HYDROXY-2-ACETYLAMINOFLUORENE (N-OH-AAF) METABOLISM BY GUNIEA PIG LIVER MICROSOMAL ENZYMES (MEETING ABSTRACT).

Vaught JB, Glowinski IB, King CM
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:330 1982

In the present studies, guinea pig liver microsomes were sonicated and subjected to gel filtration. The column fractions were analyzed for the following activities: (i) colorimetric determination of N-OH-AAF deacylation (ii) catalysis of binding of radiolabeled N-OH-P and N-OH-AAF to (transfer) tRNA (iii) high performance liquid chromatographic (HPLC) determination of metabolism of N-OH-P and N-OH-AAF. The assays for N-OH-AAF deacylation and N-OH-P binding revealed a single peak of activity (peak I). N-OH-AAF binding activity, however, was catalyzed by two peaks (I and II), peak II having a smaller molecular weight. HPLC analysis revealed that metabolism by peak I resulted in about 80% of the arylhydroxamic acids being deacylated to the corresponding nitroso derivatives, through spontaneous oxidation of arylhydroxylamines. Relatively little metabolism (less than 10%) of N-OH-P or N-OH-AAF to deacylated metabolites occurred in the presence of peak II. The data indicate that N-OH-P and N-OH-AAF are activated to nucleic acid binding metabolites by different mechanisms in this system, which are not reflected in differences in the conversion to deacylated metabolites. Nitroso-phenetole and nitroso-fluorene are known to be direct-acting mutagens, making their detection in a biological system of possible relevance to the carcinogenicity of arylhydroxamic acids. (no Refs)

16. STRUCTURE-SPECIFIC DINITROTOLUENE (DNT) PROMOTION OF INITIATED HEPATOCYTES (MEETING ABSTRACT).

Leonard TB, Lyght O, Popp JA
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:399 1982

Technical grade DNT (tDNT), containing principally the 2,4-(76%) and 2,6-(20%) isomers, is a potent hepatocarcinogen when fed to male F-344 rats for 1 yr (100% incidence). These studies were designed to assess the promoting activity of 2,4- and 2,6-DNT. Male F-344 rats were initiated with a single dose of diethylnitrosamine (DEN) (150 mg/kg; ip) or saline (controls) then fed either 2,4-DNT (27 mg/kg/day) or 2,6-DNT (10 mg/kg/day) for 12 wk. Promoting activity was quantitated by determining the number of histochemically identifiable gamma-glutamyl transpeptidase positive (GGT+) foci. Feeding 2,4-DNT to DEN initiated animals markedly increased GGT+ foci (546/cm(3)) relative to controls (0/cm(3)). Whereas 2,4-DNT alone had little effect on foci incidence, feeding 2,6-DNT alone significantly elevated the background incidence of GGT+ foci (571/cm(3)). When combined with DEN initiation, 2,6-DNT enhanced the number (867/cm(3)) but not the average diameter of GGT+ foci present. These results, together with previously reported initiation data, support the conclusion that 2,6-DNT is a potent hepatocarcinogen with both initiating and promoting activity. In addition, these data indicate that 2,4-DNT also has hepatic promoting activity which likely contributes to DNT carcinogenesis. In conclusion, the carcinogenic activity of tDNT is largely accounted for by the initiating and promoting activity of 2,6-DNT. (no Refs)

FLUORENAMINES: IN VIVO

17. ISOLATION AND TRANSPLANTATION OF PRECURSORS IN HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Miller SB, Pretlow TP, Pretlow TG

Department of Pathology, Schools of Medicine and Dentistry, University of Alabama in Birminghan, Birmingham, AL

Lab Invest; 46(1):57A 1982

The role of cells frequently termed putative preneoplastic cells in hepatocarcinogenesis is still unclear. Two types of cells widely regarded as possible precursors of hepatomas are the 'enzyme-altered hepatocyte' and the 'oval cell'. Both of these cells have histochemically demonstrable gamma-glutamyl transpeptidase (GGT). We have attempted to isolate each of these cell types free of the other to test their biologic potentials. Half a billion liver cells were purified by velocity sedimentation in the Dupont-Sorvall TZ-28 reorienting zonal rotor. When purified preparations of 98.8 per cent hepatocytes were injected into the mesenteric veins of syngeneic rats fed a diet with 0.02 per cent acetylaminofluorene and subjected to partial hepatectomy, all rats developed foci of cells with GGT in their livers in 10 days. Type II cells, small cells with intense GGT, were purified in an isokinetic gradient followed by free-flow electrophoresis. Preparations with 37.2 per cent type II cells and only 1.6 per cent hepatocytes were injected into syngeneic hosts prepared as described above. Recipients of type II cells also developed hepatic foci with GGT within 10 days. Both enzyme-altered hepatocytes and type II cells make up part of what previously has been referred to as 'liver colony-forming units'. (no Refs)

18. PURIFICATION AND TRANSPLANTATION OF PUTATIVE PRENEOPLASTIC CELLS IN HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Miller SB, Pretlow TP, Pitts AM, Pretlow TG

University of Alabama in Birmingham, Birmingham, AL, 35294

Fed Proc; 41(3):378 1982

Numerous invetigators have proposed two types of cells as possible precursors of hepatoma: the 'enzyme-altered hepatocyte' and the 'oval cell'. Both have histochemically demonstrable gamma-glutamyl transpeptidase (HDGGT). We have purified each cell type free of the other and have tested the biological potential of each. Hepatocytes were purified by velocity sedimentation in the Sorvall TZ-28 reorienting zonal rotor. Preparations containing 98.8% hepatocytes were transplanted via a mesenteric vein into syngeneic rats subjected to partial hepatectomy and fed a .02% acetylaminofluorene diet. When sacrificed 10 days later, all rats had developed foci with HDGGT. 'Type II' cells, small cells with HDGGT that probably are oval cells, were purified by a two step process of isokinetic gradient centrifugation followed by free-flow electrophoresis. Preparations with 37.2% type II cells and only 1.6% hepatocytes were obtained and injected into syngeneic hosts as described above. These animals also developed colonies with HDGGT when examined at 10 days. No similar foci were observed in animals treated identically except that they received no cells. Enzyme-altered hepatocytes and type II cells make up part of what have been referred to as 'liver colony forming units'. (no Refs)

19. SIALIC ACID METABOLISM IN NUTRITIONALLY-MODULATED HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Fox OF, Kishore GS, Graham SA, Carubelli R

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Fed Proc; 41(3):337 1982

The sialic acid content and the activities of the enzymes responsible for the activation, transfer and hydrolysis of sialic acid were investigated in the livers of male Sprague-Dawley rats treated with 2-acetylaminofluorene (AAF). Basal diets containing 20% corn oil, 18% coconut oil + 2% linoleic acid or 2% linoleic acid, with or without supplementation with 0.7% (w/w) butylated hydroxytoluene (BHT) were used. The carcinogenic diets contained 0.05% (w/w) AAF. AAF-treated rats and age-matched controls fed basal diets, were killed after 14-17 weeks of treatment. The livers were used for histological, chemical and enzymological studies. Rats fed high-fat diets showed earlier and higher incidence of AAF-induced hyperplastic nodules (HPN); BHT supplementation greatly retarded the development of these lesions. Increases in sialic acid content and in the levels of CMP (cytosine monophosphate)-sialic acid synthetase and neuraminidase, both cytosolic and particulate, were observed in the livers from AAF-treated rats. Sialyltransferase activity, on the other hand, was not affected. BHT supplementation resulted in lower levels of sialic acid and CMP-NANA synthetase in rats fed low fat and saturated-fat diets; proportional reductions were observed in AAF-treated and in control rats. The chemical and enzymatic changes observed in AAF-treated rats are consistent with an increased turnover of sialoglycoconjugates during the carcinogenic process. (no Refs)

20. 2-ACETYLAMINOFLUORENE (AAF) DEPENDENT INCREASES IN EPOXIDE HYDROLASE: SPECIES, STRAIN AND SEX DIFFERENCES (MEETING ABSTRACT).

Graichen ME, Dent JG

Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709

Toxicologist; 2(1):101 1982

Exposure of rats to hepatocarcinogens causes substantial increases in hepatic microsomal epoxide hydrolase (EH) activity. The potency of compounds in increasing EH is related to their carcinogenic potency. The objective of this study was to investigate the relationship between hepatocarcinogenicity and increases in epoxide hydrolase using the known species, strain and sex differences in susceptibility to AAF carcinogenicity. Following administration of AAF in the diet or via ip injections, liver microsomes or 10,000 g supernatant was prepared. EH activity was measured with benzo(a)pyrene-4,5-oxide as substrate. Three daily ip injections of AAF, at doses between 5 and 80 mg/kg/day, caused dose-related increases in EH in male F-344 and CD rats. The log-linear dose response obtained has the same slope in both strains and the ED50 was 13 mg/kg/day. The maximum increase observed was 350% of control activity in both strains. No increase in EH activity was detected in guinea pigs treated with AAF at doses between 40 and 240 mg/kg/day for 3 days. In DBA2 and C57Bl6 mice fed 0.02% AAF for 2 weeks, decreases in EH were observed. By comparison, F-344 male rats fed this diet exhibited a 460% increase in EH activity. Female rats, mice and guinea pigs are poor N-hydroxylators of AAF and are resistant to the carcinogenic action of AAF. (no Refs)

21. INCREASED URIDINE DIPHOSPHATE-GLUCURONYLTRANSFERASE ACTIVITY IN PRENEOPLASTIC LIVER NODULES AND MORRIS HEPATOMAS.

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Cancer Res; 42(9):3747-3752 1982

In preneoplastic rat liver nodules produced by 2-acetylaminofluorene, certain uridine diphosphate-glucuronyltransferase (UDP-GT) activities, which are ascribed to a distinct enzyme form, were selectively increased (5-fold). This enzyme form, operationally termed UDP-GT1, accepts 1-naphthol,4-methylumbelliferone, and 3-hydroxybenzo(a)pyrene as substrates and is chiefly inducible in liver by 3-methylcholanthrene-type inducers. Glucuronidation of other substrates (morphine, 4-hydroxybiphenyl, chloramphenicol, bilirubin, and estrone) was only slightly enhanced or decreased in nodular tissue. Differentially increased UDP-GT1 activities were also found in Morris hepatomas 9121 and 7777. Rabbit antibodies to rat liver UDP-GT1, purified from 3-methylcholanthrene-treated rats, demonstrated immunological similarity between the enzymes from liver, nodular tissue, and Morris hepatoma 9121. Rocket immunoelectrophoresis ascertained that enhanced enzyme activity in nodular tissue reflected an increased level of enzyme protein. Increased activity of UDP-GT1 together with decreased cytochrome P-450-dependent monooxygenase may contribute to the resistance of preneoplastic hepatocytes to the cytotoxic actions of chemical carcinogens. (Author abstract) (43 Refs)

22. SEX STEROID HORMONES LEVELS AND TESTICULAR ACTIVITY DURING HEPATOCARCINOGENESIS BY N-2-FLUORENYLACETAMIDE.

Lafaurie M, Aussel C, Castelli D, Krebs B, Stora C
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Res Commun Chem Pathol Pharmacol; 37(1):49-63 1982

During hepatocarcinogenesis by N-2-fluorenylacetamide, the hormonal status of male Sprague Dawley rats is modified. The testes present a reduced activity which is evidenced by a decreased spermatogenetic activity accompanied by a drastic decrease of the plasma testosterone level. In contrast, plasma progesterone and estradiol-17beta levels were not modified despite the 80 fold augmentation of alpha-fetoprotein, an estrogen binding protein synthesized during liver carcinogenesis. (Author abstract) (27 Refs)

23. ENZYMATIC REMOVAL OF RING OPENED ALKYLATED GUANINES FROM DNA (MEETING ABSTRACT).

Chetsanga CJ, Batenjany M, Mainwaring M
University of Michigan-Dearborn, Dearborn, MI, 48128
Fed Proc; 41(3):927 1982

We have been studying the effects of a number of carcinogens that bind to either the N-7 or C-8 position of guanine on the subsequent fate of such alkylated guanines in DNA. An interesting finding, also corroborated by other laboratories, has been that the binding of bulkier alkylating agents like phosphoramide mustard (N-7 site), aflatoxin B1 (N-7), and aminofluorene (C-8) to guanine results in imidazole ring fission at the C8-N9 bond in 20% of guanine adducts at neutral pH. With 7-methylguanine or 7-ethylguanine, ring fission to generate formamidopyrimidine only occurs in alkali. The DNA glycosylase that we earlier reported to remove ring opened 7-methylguanines from DNA also removes guanines that spontaneously undergo ring fission at pH 7.2 when alkylated by bulky alkyl groups. The ring fission in 7-methylguanine first converts C-8 to formyl groups some of which are lost until equilibrium is established between formylated and deformylated ring opened guanine adducts. The DNA glycosylase excises the formylated species of ring opened 7-methylguanine. The enzyme also excises the non-formylated ring opened guanines containing bulky alkylating groups at the C-8 position. Our results suggest that such bulky substituent groups may provide an environment conducive to stereospecific recognition of ring opened guanine adducts by the enzyme. (no Refs)

24. INDUCTION OF A NEW CLASS OF ESTROGEN-DEPENDENT MESENCHYMAL TUMORS IN RABBITS (MEETING ABSTRACT).

Galt RM, Coogan PS, Laing GH, Newton JJ, Hass GM
Rush University, Chicago, IL, 60612
Fed Proc; 41(3):330 1982

One hundred and fifty-six young virgin female (F) and male (M) albino rabbits, divided into groups, were placed on regimens, permuting the following urogenital tumorigenic factors: 240 mg% dietary 2-AAF (2-acetylaminofluorene); gonadectomy (G); 25 mg pellet sc of 17 beta estradiol (Progynon) (E2); 25 or 50 mg im weekly of medroxyprogesterone (Depo-Provera) (P). Pathologic studies showed frequently unique benign multicentric neoplasms of the spleen, kidneys and liver with occasional malignant transformation of those in the spleen. Though there was no proof of common histogenesis, all were composed of large clear pleomorphic undifferentiated mesenchymal cells, productive of a loose glycoprotein-rich intercellular matrix. Tumors occurred at random in spleen and liver but only distally in medullary renal pyramids. Induction required E2 though malignant transformation also required 2-AF, two factors favorable for induction of urogenital tumors. However, occurrence of urogenital tumors was eliminated by the best regimens for induction of the extra-urogenital neoplasms; namely, combinations of 2-AAF, E2 and P. For example, among 16 F and 10 M on these regimens for 21-69 weeks, 20 had splenic tumors of which 7 were malignant, 6 had renal tumors and 2 had liver tumors. Therefore, progesterone was the principal mediator of high incidence of these unique estrogen-dependent mesenchymal tumors in spleen, liver and kidneys of rabbits. (no Refs)

25. EARLY BIOCHEMICAL EVENTS COMPARING 2-ACETYLAMINOFLUORENE HEPATOCARCINOGENESIS AND 4-ACETAMIDOPHENOL HEPATOTOXICITY IN THE RAT (MEETING ABSTRACT).

Sawick DP, Elliott WL, DeFrees SA, Heinstein P, Cassady JM, Morre DJ
Department of Medicinal Chemistry, Purdue University, West Lafayette, IN, 47907
Proc Am Assoc Cancer Res; 23:209 1982

This study compares pyrimidine biosynthetic alterations of dihydroorotate dehydrogenase, uridine-5'-diphosphate kinase (UDP kinase), cytidine-5'triphosphate synthetase (CTP synthetase); and gamma-glutamyl transpeptidase in livers of rats fed 0.025% of the hepatocarcinogen 2-acetylaminofluorene (AAF) or 1.87% of the hepatotoxin, 4-acetamidophenol (AAP) in their diets. Results showed that within three days of AAF feeding dihydroorotate dehydrogenase specific activity was decreased to 0.6 of control while UDP kinase was increased 2.7-fold. After 14 days, a 2-fold increase in the activity of CTP synthetase was observed and by day 21 gamma-glutamyl transpeptidase specific activity was increased 8-fold. Histologically, acute centrilobular necrosis was observed in the livers of AAP fed animals. Yet no biochemical alterations resembling those induced by AAF were obtained. Dithydroorotate dehydrogenase specific activity was increased slightly as a result of hepatotoxicity but was decreased in hepatocarcinogenesis. UDP kinase and gamma-glutamyl transpeptidase specific activities were unaffected by AAP. CTP synthetase specific activity, elevated in hepatocarcinogenesis, was decreased slightly in hepatoxicity. (no Refs)

26. THE ROLE OF METABOLISM IN 2-ACETYLAMINOFLUORENE (AAF) DEPENDENT ELEVATION OF HEPATIC EPOXIDE HYDROLASE (EH) ACTIVITY (MEETING ABSTRACT).

Graichen ME, Dent JG
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:326 1982

Treatment of male rats with the hepatocarcinogen AAF causes substantial increases in hepatic microsomal EH activity. AAF is metabolized to N-hydroxy-2-acetylamino-fluorene (NOHAAF), which then can proceed either through sulfation or deacetylation pathways. These studies were designed to assess the role of the route of metabolism of AAF in elevating EH activity. Benzo(a)pyrene-4,5-oxide substrate was used to measure EH activity in post-mitochondrial supernatant prepared from the livers of male F-344 rats 48 hours after a single ip injection of AAF or NOHAAF. NOHAAF was found to be the more potent enhancer of EH activity, with an ED50 of 12 mg/kg vs 20 mg/kg for AAF. Pretreatment of male rats with Na_2SO_4 increased the EH response to 15 mg/kg NOHAAF (ED70) from 280% to 322% of control, while pretreatment with pentachlorophenol, an inhibitor of sulfotransferase, decreased the EH response to 220% of control. Pretreatment with bis(p-nitrophenyl)phosphate or isoniazid, inhibitors of deacetylation, caused no significant changes in the response to NOHAAF. None of the pretreatments alone had any effect on EH activity. Female CD rats have lower endogenous levels of sulfotransferase than female F-344 rats; treatment with 18 mg/kg NOHAAF raised EH levels to 391% of control in F-344 females but only 139% in CD females. (no Refs)

27. ISOLATION AND CHARACTERIZATION OF A NEW FUCOGANGLIOSIDE ACCUMULATED IN PRECANCEROUS RAT LIVER AND IN RAT HEPATOMA INDUCED BY N-2-ACETYLAMINOFLUORENE.

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J Biol Chem; 257(13):7698-7703 1982

A novel fucoganglioside has been found to be accumulated in the liver of rats fed N-2-acetylaminofluorene before development of hepatoma. This new fucoganglioside persisted in hepatoma in vivo but was completely absent in normal rat liver as well as in livers of rats fed the nonhepatic carcinogen, acetylaminophenanthrene, and a tumor promoter, trichloro-2,2-bis-(chlorophenyl)ethane. The ganglioside was isolated by high performance liquid chromatography and the structure was determined by methylation analysis, sequential degradation by various exoglycosidases, and by direct probe mass spectrometry of the permethylated derivative. This ganglioside, present in precancerous liver and in hepatoma in vivo, was identified as having a new structure with a substitution identical with blood group B determinant. A second fucoganglioside was detected in lower quantity in precancerous liver and in hepatoma in vivo but not in control tissue. This ganglioside co-migrated with the fucoganglioside isolated from H-35 hepatoma cells in vitro whose structure was identified as fucosylated GM1 ganglioside (Fucalpha1 to 2Galbeta1 to 4GalNAcbeta1 to 4 [NeuAcalpha2 to 3]Galbeta1 to 4Glcbeta1 to 1Cer). The results indicate that synthesis of new fucolipids is already induced at an early stage during the process of chemical carcinogenesis in rat liver which could be a unique membrane marker for diagnosis and therapy of a hepatoma and its premalignancy. (Author abstract) (45 Refs)

FLUORENAMINES: IN VITRO

28. LACTATIONAL INDUCTION OF HYDROXYLATION OF CARCINOGENS IN SUCKLING RATS BY INDUCERS OF CYTOCHROME P1-450 (MEETING ABSTRACT).

Malejka-Giganti D, Ritter CL, Decker R
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Fed Proc; 41(3):1425 1982

Modification of carcinogen metabolism in suckling young (SY) through lactational transmittal of pharmacologically active compounds is of considerable interest. We have examined the effects of ip injections to lactating rats (LR) of 3-methylcholanthrene (3-MC) or beta-naphthoflavone (beta-NF) (40 mg/kg of b wt in corn oil for 3 days) on enzyme activities of hepatic microsomes (HM) of their SY. The levels of cytochromes P-450 (P1-450) and b_5 and activities of NADH- and NADPH-cytochrome c reductases were similar to those of HM of SY from corn oil-treated LR. The apparent induction of cytochrome P1-450 in HM of SY of 3-MC- or beta-NF-treated LR was shown by the increased hydroxylations of benzo[a]pyrene (B[a]P) and N-2-fluorenylacetamide (2-FAA). In the presence of 0.1 mM alpha-NF (alpha-naphthoflavone), the levels of hydroxylation of B[a]P or 2-FAA were similar in all 3 sets of SY and were 2.7-or 5.0-fold greater, respectively, than their basal levels. This suggests that although alpha-NF in vitro stimulates the basal hydroxylating enzyme activities, it inhibits the cytochrome P1-450-induced activities as it does in HM of LR. In the latter, alpha-NF was a more potent inhibitor than beta-NF. Binding to HM showed that beta-NF (type I) binds with a higher affinity than the type I substrates B[a]P and 2-FAA, whereas alpha-NF gives a qualitatively different binding spectrum suggestive of multiple binding sites. (no Refs)

29. ROLE OF DEPURINATION IN MUTAGENESIS BY CHEMICAL CARCINOGENS.

Schaaper RM, Glickman BW, Loeb LA
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Cancer Res; 42(9):3480-3485 1982

The effect of modifying phichi174 viral DNA by the chemical carcinogens beta-propiolactone, N-acetoxyacetylaminofluorene and anti-benzo[a]pyrene diol-epoxide was investigated by transfecting the modified DNA into Escherichia coli spheroplasts. Modification of the DNA in vitro by each of these agents was mutagenic for the phichi174 amber mutants am3 and am86. Mutagenicity depended on the induction of the 'SOS' response and the host spheroplasts. Heating beta-propiolactone-treated DNA at neutral pH caused strong inactivation such that the number of lethal hits was increased four-fold. Sucrose gradient analysis showed the induction of alkali-labile sites in the heated DNA. The 'nicked circle assay' with double-stranded phichi174 DNA showed greater than 70% of these sites to be apurinic sites. Concomitantly with the production of these new sites, a strong increase in the mutation frequency was observed. This mutagenesis also depended upon the induction of the error-prone SOS response in the spheroplasts, as was previously shown to be the case for mutagenesis at putative apurinic sites induced directly by acid-heat treatment. These results suggest that depurination may be of importance to the mechanism of mutagenesis by beta-propiolactone and other carcinogens. (Author abstract) (25 Refs)

30. CELL CYCLE REGULATION OF DNA REPAIR (MEETING ABSTRACT).

Gupta PK, Sirover MA
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Med Pediatr Oncol; 10(1):101 1982

The capacity of human cells to modulate DNA repair pathways were examined. Synchronous cultures of WI-38 normal diploid fibroblasts were to investigate whether DNA repair pathways were modulated during the cell cycle. Two criteria were used: 1) unscheduled DNA synthesis (UDS) in the presence of hydroxyurea after exposure to ultraviolet light; to N-acetoxy-acetylaminofluorene (N-AcO-AAF); to methyl methanesulfonate (MMS); or to sodium bisulfite; and 2) repair repli-

cation into parental DNA in the absence of hydroxyurea. DNA repair measured as UDS after UV irradiation or after exposure to N-AcO-AAF was induced 2-3 fold in WI-38 fibroblasts during the cell cycle reaching a maximum in cultures exposed 14-15 hrs after stimulation. Base excision repair measured after exposure to MMS or sodium bisulfite was similarly stimulated and reached a maximum at an interval of 18 hrs in the cell cycle. Similar results were observed using repair replication into parental DNA in the absence of hydroxyurea. In either instance DNA repair was sequentially stimulated prior to the induction of DNA replication which was maximal at an interval of 22-24 hrs of the cell cycle. These results suggest that normal human cells stimulate DNA repair pathways prior to DNA replication to remove DNA lesions before DNA is copied. This would ensure the transfer of correct genetic information to daughter cells and may provide a mechanism by which human cells seek to reduce mutagenesis or carcinogenesis after exposure to environmental agents. (no Refs)

31. KINETIC EVIDENCE FOR THE INVOLVEMENT OF MULTIPLE FORMS OF CYTOCHROME P-450 IN THE METABOLISM OF ACETYLAMINOFLUORENE (AAF) (MEETING ABSTRACT).

McManus ME, Minchin RF, Sanderson N, Wirth PJ, Thorgeirsson SS
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):1402 1982

In order to initiate carcinogenesis AAF requires metabolic activation. N-Hydroxylation is considered to be obligatory for this activation while ring hydroxylations appear to be detoxification pathways; all these reactions being cytochrome P-450 dependent. For an estimate of the significance of these pathways in the metabolism of AAF, a kinetic study was undertaken using rat liver microsomes and substrate concentrations ranging from 0.02-200 uM. N-Hydroxylations accounted for approximately 50% of the metabolites at low substrate concentrations (less than 0.2 uM) but less than 5% at concentrations of AAF above 10 uM. The Km and Vmax for this reaction were 0.04 uM and 5.95 pmoles/min/mg respectively. While N-hydroxylation was best described by a single enzyme system, two enzyme kinetics were observed for 1, 3, 5 and 7 hydroxylations. For example, Hofstee plots revealed a high affinity low capacity (4.87 pmoles/ min/mg) enzyme and a low affinity high capacity (1289 pmoles/min/mg) enzyme for the 7-hydroxylation of AAF. These data indicate that more than one form of cytochrome P-450 is involved in each of the ring hydroxylations, whereas only one form catalyzes the N-hydroxylation. (no Refs)

32. THE TERATOGENICITY OF 2-ACETYLAMINOFLUORENE AND SEVERAL DERIVATIVES IN VITRO (MEETING ABSTRACT).

Faustman-Watts E, Greenaway JG, Fantel AG, Juchau M
Department of Pharmacology and Pediatrics, University of Washington, Seattle, WA, 98195
Fed Proc; 41(3):1574 1982

The teratogenicity of 2-acetylaminofluorene (AAF), N-hydroxy-2-acetylaminofluorene (N-OH-AAF), N-acetoxy-2-acetylaminofluorene (AAAF), 2-nitrosofluorene (NF) and N-hydroxy-aminofluorene (N-OH-AF) have been examined in vitro. Ten-day Sprague-Dawley rat embryos were explanted and cultured for 24 hours. Exposure to AAF did not cause malformations at concentrations up to 75 ug/ml in the absence of the P-450 dependent oxidizing system; however addition of such a system to the culture media resulted primarily in neural tube abnormalities. When embryos were exposed to N-OH-AAF, AAAF, NF or N-OH-AF in vitro, malformations were produced directly in the absence of a monooxygenase system. Exposure of embryos to N-OH-AAF or AAAF at concentrations of 25 ug/ml in malformations of the prosencephalic region in approximately 50% of the exposed embryos. Embryos exposed to NF or N-OH-AF at concentrations of 25 ug/ml caused primarily abnormalities of flexure in over 60 and 85% of the embryos respectively. None of the AAF derivatives tested appeared to be solely responsible for the neural tube abnormalities observed with monooxygenease generated AAF metabolites. This suggested the possibility that other metabolites or combinations of metabolites may participate in the AAF-induced neural tube abnormalities. (no Refs)

33. REPAIR AND MUTAGENESIS OF PLASMID DNA MODIFIED BY ULTRAVIOLET IRRADIATION OR N-ACETOXY-N-2-ACETYLAMINOFLUORENE.

Schmid SE, Daune MP, Fuchs RP
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Proc Natl Acad Sci USA; 79(13):4133-4137 1982

Plasmid DNA was modified in vitro to various extents with N-acetoxy-N-2-acetylaminofluorene or UV irradiation. The modified plasmid DNAs were then used to transform Escherichia coli strains having different repair capabilities. Both survival and mutagenesis frequencies of the plasmid were measured as a function of the number of lesions per plasmid molecule. The majority of N-2-acetylaminofluorene (AAF) adducts, like thymine dimers, were repaired by the excision (uvrA+-dependent) pathway. In rec+ strains, dose-dependent mutagenesis occurred in either AAF- or UV-modified plasmid DNA. This is in contrast with results obtained in recA- strains, in which only AAF adducts gave rise to a lower, but dose-dependent, mutagenesis frequency. In these recA- strains there was no UV mutagenesis. Unlike what is observed with phages, induction of the 'SOS' functions by UV irradiation of the bacteria prior to transformation did not increase the survival or the mutagenesis of the plasmid. (Author abstract) (47 Refs)

34. N-2-ACETYLAMINOFLUORENE MODIFICATION OF POLY(DG-M5DC).POLY(DG-M5DC) INDUCES THE Z-DNA CONFORMATION.

Santella RM, Grunberger D, Nordheim A, Rich A
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Biochem Biophys Res Commun; 106(4):1226-1232 1982

Carcinogen induced conformational changes and the effect of N-2-acetylaminofluorene (N-Aco-AAF) modification on poly(dG-m5dC).poly(dG-m5dC) were investigated. The circular dichroism spectra of poly(dG-m5dC).poly(dG--m5dC) with various levels of acetylaminofluorene (AAF) modification are presented. With increasing levels of AAF, a decrease in the positive band at 280 nanometer (nm) and an increase in the negative band at 255 nm was observed. A sample with 3.5% modification underwent the B to Z transition with increasing Mg++ concentrations. A DNA sample modified with [14C] labeled AAF to an extent of 8.5% showed approx 50% digestion with S1 nuclease after 3 hr. In contrast, a 17.5% AAF modified sample of poly(dG-m5dC).poly(dG-m5dC) showed only 14% digestion after 3-hr incubation with S1 nuclease. The equilibrium binding level of the various polymers as a function of the concentration of N-Aco-AAF was determined. At the lowest concentration of N-Aco-AAF added, the methylated polymer was modified to a level of 6% compared to 3% with the unmethylated polymer. At higher concentrations of N-Aco-AAF, the level of AAF binding in the methylated polymer rose more rapidly than in the unmethylated polymer. Thus, the order of reactivity with AAF is poly(dG-m5dC).poly(dG-m5dC) greater than poly(dG-dC).poly(dG-dC) greater than poly(dG).poly(dC). Results indicated that the alternating polymer poly(dG-m5dC).poly(dG-m5dC) undergoes the B to Z transition at lower levels of AAF modification (10%) than required to convert the non methylated polymer (greater than 20%). (18 Refs)

35. THE CO-OXIDATION OF 2-AMINOFLUORENE DURING PROSTAGLANDIN BIOSYNTHESIS IN RAM SEMINAL VESICLE MICROSOMES (MEETING ABSTRACT).

Boyd JA, Eling TE
National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:78 1982

The metabolism of the chemical carcinogen 2-aminofluorene (2-AF) during prostaglandin biosynthesis, using ram seminal vesicle microsomes as a source of prostaglandin endoperoxide synthetase (PES), was examined. 2-AF inhibited prostaglandin biosynthesis in a dose-dependent manner, as well as the peroxidatic co-oxidation of phenylbutazone, suggesting that 2-AF is both an inhibitor of PES and a reducing co-factor for the hydroperoxidase activity of PES. At a concentration of 100 uM, 2-AF was co-oxidized during prostaglandin biosynthesis to 2-nitrofluorene and 2,2'-bisazoxyfluorene, both of which were isolated and identified by co-chromatography and mass spectrometry. The formation of 2,2'-bis-azoxyfluorene indicated the formation of N-OH-2-AF as well. This 2-AF metabolism was dependent on the presence of the PES substrate arachidonic acid, inhibited by the PES inhibitor indomethacin, and was not observed using heat denatured microsomal protein. Preliminary data suggest that N-OH-2-AF is also a substrate for PES, and is metabolized to 2-nitrofluorene and 2,2'-bisazoxyfluorene as well. In addition, 2-AF was metabolized to a mutagenic metabolite(s), as measured by using RSV as an activating system in the Ames test. In summary, the above data indicate that the co-oxidation of 2-AF during prostaglandin biosynthesis in vitro results in the formation of N-OH-2-AF, the presumed ultimate carcinogenic metabolite of 2-AF and 2-acetylaminofluorene. (no Refs)

36. INHIBITION OF DNA METHYLTRANSFERASE ACTIVITY BY A RANGE OF PROXIMATE CARCINOGENS (MEETING ABSTRACT).

Wilson VL, Jones PA
Childrens Hospital of Los Angeles, Los Angeles, CA, 90054
Proc Am Assoc Cancer Res; 23:259 1982

We have recently developed a method for the production of hemimethylated DNA, which can serve as an efficient methyl acceptor in a DNA-methyltransferase assay system. This hemimethylated DNA was used to determine the effects of DNA modification and adduct formation by proximate carcinogens, on in vitro enzymatic methylation of cytosine residues in DNA. Mouse spleen DNA-methyltransferase activity was markedly decreased by alkylation of hemimethylated DNA with prototypes from several classes of chemical carcinogens. Pretreatment of hemimethylated DNA with nitrogen mustard or melphalan, at a molar ratio of 0.2, resulted in a more than 50% inhibition of DNA methyltransferase activity. On a molar basis, benzo[a]pyrene diolepoxide and N-acetoxy-N-acetyl-2-aminofluorene were approximately one-tenth as potent as nitrogen mustard. The ethylating and methylating agents were the least potent in this inhibitory action. Extensive dialysis of the alkylated substrate DNA did not alter the subsequent inhibition of DNA-methyltransferase activity. Thus the formation of DNA adducts can effectively attenuate the enzymatic methylation of DNA in vitro. However, direct modification of the DNA-methyltransferase enzyme by some of these alkylating agents, was also found to significantly inhibit enzymatic activity. (1 Ref)

37. MICROSOMAL METABOLISM OF THE CARCINOGEN, N-2-FLUORENYLACETAMIDE (2-FAA), IN THE RAT MAMMARY GLAND (MEETING ABSTRACT).

Ryzewski CN, Malejka-Giganti D, Polovina M
Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455
Proc Am Assoc Cancer Res; 23:308 1982

Studies of metabolism of 2-FAA in its extrahepatic target were made possible with our new high performance liquid chromatographic method which overcomes previous difficulties in quantitative elution of N-hydroxy-2-FAA and concomitant separation of 8 other metabolites of 2-FAA. Peak detection is by UV absorbance and quantitation is by peak area determination relative to standard curves. We have determined the products which form during incubation of 2-FAA with mammary gland microsomes (MGM) of lactating rats treated with corn oil (control) and 3-methylcholanthrene or beta naphthoflavone. These compounds induced cytochrome P1-450 in MGM and hepatic microsomes (HM). Overall metabolism, indicated by decreases in substrate, was slower in MGM than in HM for equivalent amounts of microsomal protein from rats treated with the inducers. MGM from control rats were capable only of hydroxylation to 9-, 5-and 3-hydroxy-2-FAA. MGM from induced rats had enhanced capacities to hydroxylate to 5-and 3-hydroxy-2-FAA and had the capacities to hydroxylate to 7-hydroxy-2-FAA and most importantly to N-hydroxy-2-FAA, the proximate mammary gland carcinogen. The capacity of MGM of induced rats to convert 2-FAA to N-hydroxy-2-FAA may be of significance in tumorigenesis not only in the mammary gland but in suckling rats as well. (no Refs)

38. METABOLIC ACTIVATION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES BY RAT ZYMBAL'S GLAND (MEETING ABSTRACT).

Allaben WT, Weis CC
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:321 1982

A target tissue for many carcinogenic aromatic amines in the rat is the Zymbal's gland. Because of recent findings that the N-propionyl derivative of N-hydroxy-2-aminofluorene (NP) was a potent carcinogen in this tissue, we have compared the in vitro metabolism of NP to the less carcinogenic N-acetyl (NA) and N-formyl (NF) derivatives. The Zymbal's glands from S/D rats were removed, homogenized and fractionated by centrifugation into the 9000 x g supernatant (S9), cytosol, and microsomes. N,O-Acyltransferase (AT) (assayed by tRNA:fluorenyl adduct formation) and deacylase (assayed by N-hydroxy-2-aminofluorene formation) activities were determined using these fractions. The cytosol was further fractionated by gel-filtration. AT assays showed activities as follow: for S9, NF greater than NP greater than NA; for cytosol, NF greater than NP greater than NA; and for microsomes, NF much greater than NA greater than NP. Paraoxon inhibited adduct formation catalyzed by the cytosol fractions for NF, and by microsomes for NF, NP, and NA. In contrast, deacylase assays were as follows: S9, NP greater than NA much greater than NF; cytosol, no activity; and microsomes, NP much greater than NA much greater than NF. All deacylase reactions were paraoxon-sensitive. Gel-filtration chromatography of cytosol demonstrated two AT's: an early eluting fraction with high specificity for NF; and a later eluting fraction exhibiting activity for NP. Relative Zymbal's gland AT activity, compared to liver AT activity, is about 0.03 for NA, 0.3 for NP and 1 for NF. Zymbal's gland deacylase activity, compared to liver deacylase activity, is about 2x for NA and about 3x for NP. Deacylation appears to be the major metabolic pathway in Zymbal's gland homogenates for NP and NA. Moreover, deacylase activity corrrelates with the tumor incidence observed in Zymbal's gland (NP greater than NA greater than NF). (no Refs)

39. ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS VIA A LIPOXYGENASE-PEROXIDASE ROUTE (MEETING ABSTRACT).

Wong PK, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Proc Am Assoc Cancer Res; 23:323 1982

The proximate carcinogen, N-hydroxy-2-acetylamino-fluorene (N-OH-AAF) was found to be metabolized into 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAc-AAF) by rat mammary parenchymal cells through a peroxidative mechanism. The detection of N-OAc-AAF and NOF as end products by high pressure liquid chromatography (HPLC), the presence of nitroxyl free radical as indicated by electron spin resonance spectroscopy (ESR) and the inhibitory actions of peroxidase inhibitors such as ascorbate and p-aminophenol strongly suggest that peroxidative oxidation is the major route operating in such a system and that neither the acyltransferase nor deacylase route occurs to any appreciable extent. Ram seminal vesicle microsomes also activate N-OH-AAF to NOF. Unlike the prostaglandin synthetase, mammary cell enzymes are not affected by indomethacin or aspirin while lipoxygenase inhibitors, 5,8,11,14-eicosatetraynoic acid (ETYA), gossypol and Fe(III) chelators such as deferoxamine inhibit the cell activity. Externally added arachidonate enhances N-OH-AAF activation. The hydroperoxides generated from exogenous and endogenous arachidonate by the lipoxygenase pathway is believed to be the substrate for the peroxidase activation mechanism. Mammary cells isolated from animals on selenium-supplemented diet are less active than cells from animals on selenium-deficient diet. As selenium was known to inhibit tumor formation on experimental animals, lipoxygenase and peroxidase activities of mammary gland cells appear to be related to mammary carcinogenesis. (no Refs)

40. COMPARATIVE MUTAGENICITY AND TERATOGENICITY IN VITRO OF 2-ACETYLAMINOFLUORENE (AAF), N-ACETOXY-2-ACETYLAMINOFLUORENE (AAAF) AND 2-NITROSOFLUORENE (NF) (MEETING ABSTRACT).

Faustman-Watts EM, Yang HL, Greenaway JG, Juchau MR
Department of Pharmacology, University of Washington, Seattle, WA, 98195
Proc Am Assoc Cancer Res; 23:365 1982

Interest in the interrelationships among the carcinogenic, mutagenic and teratogenic effects of chemicals has increased markedly and these were investigated by examining the mutagenic and teratogenic effects in vitro of AAF and two of its potent mutagenic metabolites. AAF displayed neither mutagenicity nor teratogenicity in the absence of a P-450-dependent monooxgenase system within the concentration ranges tested. Mutagenicity was assessed by measuring back-mutations of Salmonella typhimurium auxotrophs; teratogenicity was assayed with explanted ten-day Sprague-Dawley rat embryos that were cultured for 24 hours in vitro. Additions of an hepatic monooxygenase system (S-9 and cofactors) resulted in the production of prominent neural tube abnormalities as well as marked mutagenicity. AAAF and NF both exhibited potent, direct mutagenic and teratogenic effects in vitro. However, NF was approximately 10-fold more active than AAAF as a mutagen but only slightly more active as a teratogen. Furthermore, AAAF produced principally prosencephalic malformations whereas additons of NF resulted primarily in abnormalities of flexure. Neither of the individual metabolites produced the same teratogenic effects as bioactivated AAF. The results indicated a separation of the mutagenic and teratogenic effects of metabolites of AAF and also demonstrated that other metabolites appear to be responsible for the observed neural tube abnormalities elicited by biotransformed AAF. (no Refs)

OTHER FUSED RING AMINES

41. ANTHRACENEDIONE ANTINEOPLASTIC AGENT INHIBITION OF MICROSOMAL DRUG METABOLISM (MEETING ABSTRACT).

Kharasch ED, Cook NI, Novak RF
Department of Pharmacology, Northwestern University Medical and Dental Schools, Chicago, IL, 60611
Fed Proc; 41(3):1573 1982

HAQ, 1,4-bis(2-[(2-hydroxyethyl)amino]-ethylamino)-9,10 anthracene-dione diacetate, has excellent antitumor efficacy but causes significantly less cardiotoxicity than Adriamycin. We showed previously that HAQ inhibited microsomal NADPH oxidation and superoxide formation with little evidence of metabolic activation. Presently, HAQ was found to inhibit N-demethylase and O-dealkylase activities in phenobarbital-induced rabbit liver microsomes and aryl hydrocarbon hydroxylase activity in beta-naphthoflavone-induced microsomes. The inhibition was noncompetitive with respect to substrate concentration with Ki's of 2.6, 2.9 and 3.0 mM respectively, for N,N-dimethylaniline, p-nitroanisole and benzo[a]pyrene. In contrast, HAQ failed to inhibit p-nitroanisole metabolism when the reaction was supported with cumene hydroperoxide. HAQ also inhibited basal and substrate-stimulated microsomal NADPH oxidation. The degrees of inhibition of NADPH oxidation and product formation were comparable. These data, in conjunction with previous studies, suggest that HAQ inhibits electron transfer by microsomal NADPH-cytochrome P-450 reductase, diminishing electron flow to cytochrome P-450. This mechanism differs markedly from that for menadione inhibition of drug metabolism in which accelerated electron flow through P-450 reductase to the quinone diverts reducing equivalents from cytochrome P-450. (no Refs)

42. ELECTRON SPIN RESONANCE STUDY ON THE METABOLISM OF 2-NAPHTHYLAMINE AND 1-NAPHTHYLAMINE IN RAT LIVER MICROSOMES.

Nakayama T, Kimura T, Kodama M, Nagata C
Biophysics Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Gan; 73(3):382-390 1982

Incubation of 2-naphthylamine (2-NA) with rat liver microsomes fortified with NADPH resulted in the formation of two types of free radicals which were identified as being due to N-hydroxy-2-naphthylamine and 2-amino-l-naphthol. The former radical was shown to be oxidized further to 2-nitrosonaphthalene radical. Compared with the case of the constitutive microsomes, the amount of the free radicals increased progressively on using the microsomes from methylcholanthrene (MC)-induced or phenobarbital (PB)-induced rats. On the other hand, the amount of the free radical formed from 1-naphthylamine (1-NA) was much less than that from 2-NA, so that the radical structure was not identified unambiguously. The enzymes involved in this case were not induced by either MC or PB. Thus, from the viewpoint of free radical formation, the metabolic patterns of 2-NA and 1-NA are quite different and such different behavior might be correlated with the distinct difference in their carcinogenicities. From the inhibitory effects of carbon monoxide, SKF-525A, alpha-naphthoflavone and 1-(1-naphthyl)-2-thiourea on the free radical formation, it was concluded that both mixed function oxidases (cytochrome P-450s) and mixed function amine oxidase (dimethylaniline monoxygenase) are involved in the metabolism of 2-NA. (Author abstract) (31 Refs)

43. ISOLATION AND STRUCTURAL DETERMINATION OF MUTAGENIC SUBSTANCES IN COAL TAR.

Kosuge T, Zenda H, Nukaya H, Terada A, Okamoto T, Shudo K, Yamaguchi K, Iitaka Y, Sugimura T, Nagao M, Wakabayashi K, Kosugi A, Saito H
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Chem Pharm Bull (Tokyo); 30(4):1535-1538 1982

Fractionation of the basic fraction of coal tar yielded 11 compounds that showed mutagenic activity in Salmonella typhimurium in the Ames test. The molecular structures of these compounds were analyzed. Six were aminopolycyclic aromatic hydrocarbons: 1-aminofluoroanthene, 1-aminophenanthrene, 3-aminophenanthrene, 1-aminopyrene, 3-aminopyrene, and 5-aminobenz[a]anthracene. Five were aza-polycyclic aromatic hydrocarbons: phenaleno[1,9-gh]quinoline, pyrido[3,2-c]carbazole, quino[3,2-c]carbazole, benzo[h]naphtho[2,1,8-def]quinoline, and benzo[de]naphtho[1,8-gh]quinoline. (7 Refs)

44. THE COOPERATIVE ROLE OF BACTERIAL AND MAMMALIAN ENZYMES IN MUTAGENIC ACTIVATION OF NITRO-PAH COMPOUNDS (MEETING ABSTRACT).

Pederson TC, Siak JS
Biomedical Science Department, GM Research Laboratories, Warren, MI, 48090
Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

The NADPH-Dependent enzyme activity in rat liver microsomes can significantly increase the mutagenicity of several nitro-substituted PAH (polynuclear aromatic hydrocarbon) compounds in the Salmonella/S9 mutation assay under appropriated assay conditions. The enhanced mutagenicity of 2-nitrofluorene (2NF), 1-nitropyrene (1NP), 6-nitrochrysene (6NC) and 6-nitrobenzo(a)-pyrene (6NBaP) in the presence of S9 enzymes can be detected using strain TA98 or the niridazole-resistant strain TA98NR. The S9-dependent activation of 6NBaP, like that of BaP, can also be observed using the dinitropyrene-resistant strains TA98/1,8-DNP6 and TA98NR/1,8-DNP2. In contrast, there is little or no detectable activation of 2NF, 1NP or 6NC by S9 enzymes in assays employing the dinitropyrene-resistant strains, suggesting that the S9-dependent mutagenicity of these compounds towards TA98 and TA98NR requires bacterial nitroreductase activity for formation of the ultimate mutagenic metabolites. This interpretation is supported by experiments with 1NP which demonstrate that an extractable mutagenic metabolite accumulates during incubation with S9 enzymes. The chromatographic and spectroscopic properties of this metabolite suggest it is a hydroxylated derivative of 1NP. It exhibits a high mutagenicity with TA98 and TA98NR but is markedly less active towards the dinitropyrene-resistant strains. There is no evidence to suggest that the S9-dependent activation of 6NBaP involves bacterial nitroreductase activity. This compound may be activated entirely by S9 enzyme activity to form a reactive product such as an epoxide. Thus, the increased mutagenicity of a nitro-PAH compound in the Salmonella/S9 assay may be either dependent or independent of bacterial nitroreductase activities. (no Refs)

45. MAMMALIAN ACTIVATION AND METABOLISM OF 1-NITROPYRENE (MEETING ABSTRACT).

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Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

We have used 1-nitropyrene (NP) as a model Nitrated polycyclic organic compound (NPOC), to investigate potential genotoxicity in mammalian systems. NP was generally non-mutagenic in bioassays conducted in Chinese hamster ovary cells, and in the mouse lymphoma L5178Y system. However with the addition of a metabolic activation system consisting of the S-9 fraction from Arochlor-induced rat liver. NP proved to be more mutagenic than benzo(a)pyrene in the latter assay. NP also induced unscheduled DNA synthesis in primary rat hepatocytes. The ability of S-9 to activate NP was confirmed by assay in the Salmonella nitro-reductase-deficient strain TA98FR1, in which NP exhibits minimal 'direct-acting' mutagenicity. S-9 increased the mutagenicity of NP seven-fold,and microsomes derived from the S-9 produced a twenty-fold increase. 1-Aminopyrene and N-acetylaminopyrene, the principal reductive metbolic products of NP, have been identified by HPLC (high performance liqiud chromatography) in incubations of NP with S-9. Other metabolites were tentatively identified as phenols produced by aromatic ring oxidation. Thus some mammalian enzyme systems are indeed capable of carrying out the metabolic reactions associated with genotoxic activity in microbes. The contribution of the oxidative metabolic products to the geno- and cytotoxicity seen in mammalian cells remains to be evaluated more closely. (no Refs)

46. MUTAGENICITY OF NITROAROMATIC HYDROCARBONS IN THE SALMONELLA ASSAY: STRUCTURE ACTIVITY RELATIONSHIPS (MEETING ABSTRACT).

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Fifth CIIT Conference on Toxicology: Toxicity of Nitroaromatic Compounds, January 28-29, 1982, Raleigh, North Carolina. Chemical Industry Institute of Toxicology 16 pp., 1982.

A selected group of nitroaromatic hydrocarbons was assayed for mutagenicity in the Salmonella histidine reversion assay and several useful conclusions were drawn, based on their chemical structure. Almost all the compounds were direct acting, in that they did not require any addition of exogenous metabolic enzymes (S-9 mix). Strains capable of detecting frameshift mutations (TA98 and TA100) were reverted by these compounds. A dependence on the carbon ring size was noted for mutagenic activity. The larger fused ring structures such as nitroperylene (5-ring) and nitropyrene (4-ring) were more mutagenic than nitronaphthalene (2-ring). Compounds with only one all-carbon ring (nitrobenzene, nitrotoluenes, nitroxylenes) were not mutagenic. However, ring substitution with nitrogen as in nitropyridine, nitrobenzimidazole and nitroquinoline resulted in significant mutagenic activities. Results obtained under aerobic and anaerobic conditions will be compared. The data presented would contribute to a growing information base on chemical structure/mutagenic activity relationships which can lead to a clearer understanding of the mechanism for biological activity. (no Refs)

47. METABOLISM OF 6-NITROBENZO(A)PYRENE BY HAMSTER EMBRYO CELLS AND RAT LIVER MICROSOMES (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:312 1982

Nitrosarenes are formed during combustion of diesel fuel. Several of these compounds are known mutagens in short-term assay and are therefore suspect as presenting a potential human risk. The metabolism of a suspected environmental contaminant, 6-nitrobenzo(a)pyrene, was studied employing hamster embryonic fibroblasts and hepatic microsomes from 3-methylcholanthrene pretreated rats to compare intact cell metabolism against cell-free systems routinely used in short-term mutagenic assays. Organic solvent-soluble metabolites were separated by high-pressure liquid chromatography. Incubation of 6-nitrobenzo(a)pyrene with hamster embryo cells gave rise to both organic and water-soluble metabolites. When ethyl acetate extract of the extracellular medium was analyzed, a major peak at the dihydroxy region was detected 24 hr after introduction of substrate to cell culture. Small amounts of a phenolic product was also obtained at this time point. Subsequent treatment of remaining aqueous phase with beta-glucuronidase, however, indicated that the majority of the phenol produced had readily been converted to water-soluble glucuronide conjugates. Intracellular metabolites of 6-nitrobenzo(a)pyrene were also detected and comprised mainly of phenolic and dihydroxy products. As a comparison to cellular metabolism, hepatic microsomes were incubated with 6-nitrobenzo(a)pyrene in the presence of NADPH. Microsomal metabolism resulted in the production of one major phenolic metabolite, which was previously found to be conjugated in the cellular system, with minor dihydroxy and quinone products. (no Refs)

AMINO AZO AND OTHER AZO COMPOUNDS

48. HEPATOTOXIC AND CANCEROUS ACTIVATION OF GAMMA-GLUTAMYLTRANSFERASE IN RAT LIVER (MEETING ABSTRACT).

Fiala S, Payne RR, Trout EC, Kettering WG, Fiala A
Cell Physiology Laboratory, Veterans Administration Medical Center, Martinsburg, WV, 25401
Med Pediatr Oncol; 10(1):103 1982

Hepatotoxic compounds benzyl chloride, gamma-hexachlorocyclohexane, carbon tetrachloride, and the pesticide Kerb, and carcinogenic 3'-Me-DAB, administered to Sprague-Dawley male rats in one or two large doses, produced in 24 hrs a striking increase in the liver of the activity of gamma-glutamyl transferase (GGT) and a definite increase of total DNA. An increase in the number of GGT (+) hepatocytes was detected histochemically. In contrast to the induction by 3'-Me-DAB of simultaneous increases of GGT and of the glutathione (GSH) concentration during the period of 24-48 hrs, the increase of GGT produced by hepatotoxic compounds was accompanied by a decrease of GSH which forced GGT to return in 48 hrs to initial values. In hypophysectomized rats hepatotoxic compounds and 3'Me-DAB produced an increase of GGT which rapidly fell to the initial level without any substantial change in the concentration of GSH. From these experiments we concluded that: 1) Increase of GGT alone is not a specific effect of hepatocarcinogens in rat liver, but can be produced by various compounds which are toxic to liver tissue; 2) Not GGT alone, but only the combination of GGT with GSH is the Marker of rat liver carcinogenesis; 3) 3'-Me-DAB inactivates the feedback which keeps the levels of GSH and of GGT constant at the normal values; 4) Hepatotoxic compounds, as long as they do not damage the GSH-GGT feedback, are not carcinogenic for rat liver; 5) In hypophysectomized rats 3'-Me-DAB does not produce tumors because in their livers it is only hepatotoxic and does not become carcinogenic. A model will be proposed of GSH-GGT feedback, its nature, and function. Hepatotoxic effect of a compound has a relatively low affinity for vital receptors and can easily be removed, so that they are not permanently changed. The cancerous effect concerns receptors not essential to the life of the cell and involved in the social rather than the vital functions. The affinity for their receptors is high. (no Refs)

49. CHARACTERIZATION AND PROPERTIES OF THE DNA ADDUCTS FORMED BY THE HEPATOCARCINOGEN N-METHYL-4-AMINOAZOBENZENE IN TARGET AND NON-TARGET ORGANS.

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University of Arkansas for Medical Sciences, Little Rock, AR
Diss Abstr Int [B]; 42(10):4005-B 1982

The carcinogenic aminoazo dyes, typified by N-methyl-4-aminozobenzene (MAB), are believed to be metabolized to electrophilic N-sulfonyloxy esters which bind covalently to cellular macromolecules, resulting in the induction of hepatic neoplasia. Since the persistence of DNA-carcinogen adducts has been demonstrated to correlate with the susceptibility of specific tissues to tumor formation, the identity and persistence of the DNA adducts formed by MAB in target (liver) and non-target (kidney and spleen) organs has been determined. In order to produce quantities of adducts sufficient for structural determination, the synthetic ultimate carcinogen, N-benzoyloxy-N-methyl-4-aminoazobenzene (N-BzO-MAB) was reacted in vitro with calf thymus DNA. After enzymatic hydrolysis of the DNA, six MAB-DNA adducts were detected by high pressure liquid chromatographic analysis. In vivo adducts corresponding to all six of the in vitro products were detected after one to five weeks of feeding diets containing 0.06% (3H)MAB. Comparison of the adducts isolated from target and non-target tissues revealed a number of differences during the treatment period; however, the only persistent alteration was the increased levels of 3-(deoxyguanosin-N2-yl)-MAB (N2-dG) in hepatic DNA. N2-dG, therefore, is the adduct most likely to be responsible for the induction of hepatic tumors by MAB. (no Refs)

50. GLUTATHIONE, LIPID PEROXIDATION AND REGULATION OF CYTOCHROME P-450 ACTIVITY.

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Life Sci; 31(8):779-784 1982

Depletion of hepatic glutathione leads to an increase in lipid peroxidation and depression of cytochrome P-450-catalyzed metabolism of the azo dye carcinogen, N,N-dimethyl-4-aminoazobenzene. This contributes to the marked decrease in biliary excretion of N-demethylated metabolites of the dye. Parallel time courses are seen for decreased hepatic glutathione, enhanced lipid peroxidation and depressed excretion of dye metabolites. In vitro metabolism of DAB by hepatic 10,000 g supernatant fractions is depressed by iron only after glutathione depletion. In view of the iron requirement for microsomal lipid peroxidation, it is proposed that glutathione depletion leads to an increase in the intracellular iron available for activation of lipid peroxidation. In this way, glutathione may contribute to the regulation of cytochrome P-450 activity. (Author abstract) (26 Refs)

51. THE EXPRESSION OF ALPHA-FETOPROTEIN AND ALBUMIN GENES IN RAT LIVER DURING CHEMICAL CARCINOGENESIS.

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Biochem Biophys Res Commun; 107(1):239-245 1982

The expression of alpha-fetoprotein (AFP) and albumin genes in neoplastic and preneoplastic livers of Fischer rats treated with the hepatocarcinogen 3'-methyl-4-dimethylaminoazobenzene (MDAB) was investigated. The concentration of AFP started to increase in the serum of rats shortly after the initiation of feeding with MDAB (0.06% of the diet). It reached a peak at about 40 days and then decreased dramatically. After 164 days of treatment, serum levels of AFP increased markedly concomitant with the appearance of palpable liver tumors. The final permanent elevation of AFP was associated with the appearance of malignant cells. There was little if any change in the serum albumin concentrations in rats treated with MDAB. Synthesis of AFP in livers of MDAB-treated rats was found to increase in parallel with AFP serum concentrations. Biosynthesis of albumin showed no changes during hepatocarcinogenesis. These results indicate alteration in the control of gene expression during neoplastic transformation. (29 Refs)

52. CHANGES OF TRYPTOPHAN PYRROLASE ACTIVITY IN LIVER OF RATS SUBJECTED TO SINGLE INJECTION OF HEPATOCARCINOGEN 4-DIMETHYL-AMINOAZOBENZENE AND ITS NONCARCINOGENIC ANALOG.

Chernyshova MD, Medvedeva ND
Lab. Cytology Tumor Growth, Inst. Cytology, Leningrad, USSR
Tsitologiia; 24(5):615-617 1982

The effect of single ip injection of hepatocarcinogen 4-dimethyl-aminoazobenzene (DAB) and its noncarcinogenic analog 4-diethyl-aminoazobenzene (DEAB) on activity of liver tryptophan pyrrolase (TP) was studied in random-bred albino rats. Both DAB and DEAB at 250 mg/g produced short-term elevation of TP activity. Progressive decrease of TP activity was observed within 4-12 days after administration. The decrease of TP activity was associated with progressive decrease of the number of differentiated cells in the liver. (14 Refs) (In RUS)

53. ELEVATION OF SERUM ALBUMIN CONCENTRATION IN ANALBUMINEMIC RATS BY ADMINISTRATION OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE.

Makino R, Esumi H, Sato S, Takahashi Y, Nagase S, Sugimura T
Biochemistry Div., Natl. Cancer Center Res. Inst., 1-1, Tsukiji 5 chome, Chuo-ku, Tokyo, Japan
Biochem Biophys Res Commun; 106(3):863-870 1982

Analbuminemic rats established from a stock of Sprague-Dawley rats were investigated for the presence of rat serum albumin and the effects of 3'-methyl-4-dimethylaminoazobenzene (DAB) on albumin content. In 4-wk-old rat sera a single radial immunodiffusion method detected a small but distinct precipitin ring that was indistinguishable from rat serum albumin (RSA) by immunoelectrophoresis. The protein had the same mol wt of 65,000 as RSA and reacted with anti-RSA IgG. Peptide mapping demonstrated that the protein was albumin-like and further investigation demonstrated that it originated from the analbuminemic rats. Treatment of the rats with DAB for 7 wk increased the serum albumin concentration to a max after 15 wk (32 ug/ml, approx 2x that of untreated rats). One rat autopsied after 18 wk of DAB treatment had a hepatic tumor. It is suggested that somatic reverse mutation of analbuminemic rat hepatocytes caused the increase of serum albumin observed after DAB treatment. (18 Refs)

54. GASTRIC CARCINOGENESIS BY 4-(HYDROXYMETHYL)BENZENEDIAZONIUM ION(TETRAFLUOROBORATE) OF AGARICUS BISPORUS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:196 1982

The aim of this investigation was to explore the tumor-inducing effect of a single oral administration of 4-(hydroxymethyl)benzenediazonium ion(tetrafluoroborate)-(4-HMBD) of the cultivated mushrooms of commerce Agaricus bisporus. For this reason, a single intragastric instillation of 400 ug 4-HMBD per g of body weight was given to Swiss albino mice. As a solvent control, sodium tetrafluoroborate (STB) was administered by the same method as above to another group of mice. Each group consisted of 100 animals. As a result of treatment, 29% of the females (3 are still living) and

28% of the males developed glandular stomach tumors, while none were observed in the solvent-instilled control groups. Histopathologically, the tumors were classified as polypoid adenomas and adenocarcinomas. This diazonium ion was detected in the aqueous extract of Agaricus bisporus at a level of 0.6 ppm. In addition, it was revealed that the ion is generated from the agaritine component of this mushroom by an enzyme system acting in situ. An earlier investigation demonstrated that when given subcutaneously to mice, 4-HMBD induced tumors of the subcutis and skin. Since the human population consumes large amounts of Agaricus bisporus, the findings carry practical environmental implications. (1 Ref)

55. FORMATION AND BIOLOGICAL PROPERTIES OF DNA ADDUCTS FROM THE HEPATOCARCINOGEN, N-METHYL-4-AMINOAZOBENZENE (MEETING ABSTRACT).

Tullis DL, Baetcke KP, Kadlubar FF
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:241 1982

In previous studies, 3 major in vivo DNA adducts of the hepatocarcinogenic aminoazo dye, N-methyl-4-aminoazobenzene (MAB), were identified. These were 3-(deoxyguanosin-N(2)-yl)-MAB (N(2)-dG), N-(deoxyguanosin-8-yl)-MAB (C8-dG), and 3-(deoxyadenosin-N(2)-yl)-MAB (N(6)-dA). To investigate the role of these adducts in tumor induction, male S/D rats were fed diets containing 0.06% [3',5'-3H]MAB (100 mCi/mmol) for 1, 3, or 5 weeks and then sacrificed at 0, 1, or 3 days after the end of the treatment period. DNA was isolated from carcinogen target (liver) and non-target (kidney and spleen) tissues, and was enzymatically hydrolyzed to nucleosides. Immediately after each treatment period, the total level of carcinogen binding to DNA was 3 to 10-fold higher in target than in non-target tissues. However, the total level of binding in the liver rapidly decreased to one-half of the original level at 3 days post-treatment. When the individual adducts from target and non-target tissues were compared at the end of each treatment period, the highest observed levels of each adduct were found in the liver. The N(2)-dG adduct was always predominant, followed by C8-dG, N(6)-dA, and an unidentified adduct. By 3 days after MAB dosing, the hepatic levels of C8-dG and the unidentified adduct had decreased 50-90% to levels similar to those found in kidney and spleen. Hepatic N(6)-dA, which in previous studies appeared to be persistent after acute doses, decreased 70-80% at 3 days after chronic treatment. In contrast, hepatic N(2)-dG remained at a high level and accounted for 10-15 adducts/10(6) nucleotides after 5 weeks of dosing. (no Refs)

56. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT-AND INDIRECT-ACTING CARCINOGENS (MEETING ABSTRACT).

Nesnow S, Garland H, Curtis G
Carcinogenesis and Metabolism Branch, US Environmental Protection Agency, Research Triangle Park, NC, 27711
Proc Am Assoc Cancer Res; 23:284 1982

C3H10T1/2CL8 cells are transformed by a variety of structurally different chemicals, including polycyclic aromatic hydrocarbons, aromatic amines, and pyrimidines. It has been reported that C3H10T1/2CL8 cells are insensitive to the transforming effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) unless the cells are synchronized. This finding is particularly interesting because MNNG mutates C3H10T1/2CL8 cells to ouabain resistance without the need for cell synchrony. Aflatoxin B1 (AFB1) also does not transform C3H10T1/2CL8 cells under conditions described by Reznikoff et al. We report here that oncogenic transformation of C3H10T1/2CL8 cells can be improved by treating asynchronous cultures of cells 5 days after seeding. Benzo(a)pyrene-induced transformation was increased fourfold by this method, compared with treating the cells 1 day after seeding. MNNG produced an average of 1 focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and AFB1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene and urethane did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. (1 Ref)

HETEROCYCLIC AMINES

57. CHRONIC TOXICITY/CARCINOGENICITY OF MEFLOQUINE-HCL (WR 142490 HCL) IN RATS AND MICE (MEETING ABSTRACT).

Korte DW, Heiffer MH, Ellis HV, Hacker MP, Hong CD, Yuan YD, Kintner LD, Lee CC
Walter Reed Army Institute Research, Washington, DC, 20012
Fed Proc; 41(3):1716 1982

Mefloquine-HCl (M) was administered as a drug-feed mixture to male and female BDF1 mice and Long-Evans hooded rats at doses of 0, 5, 12.5 or 30 mg/kg/day for 2 years. All mice tolerated the treatment regimen well with significant changes occurring only at the high dose. Male mice had a decreased body weight versus control and females had an increased incidence of deaths. The primary histopathological observation was an increased incidence of gastritis in the high dose animals. In rats, the high dose of M caused a decrease in weight, an increased incidence of deaths, hind limb paralysis in males, and vaginal hemorrhage. Changes in hematological indices included a decrease in RBC, HCT (hematocrit) and Hb and an increase in reticulocytes and WBC. Clinical chemistry changes were observed only at the high dose and included increased SGOT, BUN (blood-urea nitrogen), and alkaline phosphatase. Dose-related histopathological changes occurred in the eye, lung, sex organs, skeletal muscle, spleen and lymph nodes, with only moderate changes in sex organs, lung and skeletal muscle present in low dose animals. There were no dose-related changes in incidence of neoplasms in rats or mice. Thus it was concluded that the rat was more sensitive to M than the mouse and that M was not carcinogenic under conditions of this study. (no Refs)

58. NEWLY SYNTHESISED DNA IN AGEING HUMAN CELLS IN CULTURE TREATED WITH 4-NITROQUINOLINE-1-OXIDE.

Cooke A, Harris WJ
Dept. Medical Genetics, Royal Hosp. for Sick Children, Yorkhill, Glasgow, Scotland
Mech Ageing Dev; 19(2):171-180 1982

Two lines of normal human embryonic lung fibroblasts, MRC-5 and F2002, were serially subcultured until senescence was attained. When cells were exposed to varying concentrations of the chemical carcinogen 4-nitroquinoline-1-oxide (4-NQO), the rate of DNA synthesis (as measured by thymidine incorporation) was reduced in a dose-dependent fashion in cells from both early and late passages. While the overall amount of incorporation was considerably lower in old cells, the extent of inhibition caused by 4-NQO treatment (relative to appropriate controls) was not related to culture age. Alkaline sucrose density gradient analysis of newly synthesised DNA from cells pretreated with 4-NQO failed to detect any significant variation in the size of labeled DNA from cells examined immediately after incubation with radioactive thymidine. The shift of this labeled material to high mol wt in 4-NQO-treated cells also showed no age-related difference. (Author abstract) (26 Refs)

59. INVESTIGATION OF THE BUTYROPHENONE TRANQUILIZER AZAPERONE AND ITS MAIN METABOLITES WITH THE SALMONELLA/MICROSOME TEST.

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Institut fur Lebensmittelchemie, Technischen Universitat Berlin, Muller-Breslau-Strasse 10, 1000 Berlin 12, W. Germany

Mutat Res; 104(6):339-344 1982

Mutagenicity of azaperone and its metabolites at several concentrations in the Ames Salmonella/microsome test using five histidine-auxotrophic strains is reported. Azaperone, azaperol (the main metabolite in swine), and metabolite C (the main metabolite in rats) were mutagenic after metabolic activation. The mechanism of the frameshift mutagenicity observed is explained by microsomal N-oxidation of the N-heterocycles. (10 Refs)

60. COMPARATIVE EXAMINATIONS OF THE NITROSATION CONTENT OF DRUGS AT CONSTANT PH AND UNDER SIMULATED STOMACH CONDITIONS.

Ziebarth D

Zentralinstitut fur Krebsforschung, AdW der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany

Arch Geschwulstforsch; 52(6):429-442 1982

The nitrosation of 60 orally administered drugs used in the German Democratic Republic was studied in order to evaluate the risks to patients receiving these drugs. Gastric juices were obtained from patients following stimulation with pentagastrin. Each of the drugs to be tested, at the highest therapeutic concentration, was exposed to nitrite in the presence of gastric juices. In the first series of tests, a constant pH of 2.0 at 37 C was maintained during an incubation time of 1 hr. In a second series, pH was varied to simulate conditions in the stomach at various phases of digestion. For 39 drugs no decrease in nitrite concentration or formation of N-nitroso compounds (NNC) could be detected. For three drugs the nitrate concentration dropped rapidly, but no NNC could be detected. For seven drugs the colorimetric methods used were inadequate because of the formation of azo compounds. For 11 drugs the nitrate concentration dropped and NNC were detectable. These drugs included aminophenazone, ampicillin, clomipramin, desipramine, ethambutole, imipramine, noramidopyrinemethanesulfonate, oxacillin, phenoxymethylpenicillin, and piperazine. Two known carcinogens, N-nitroso-dimethylamine and N-nitroso-piperazine, were identified among the nitrosation products. The remaining products have not been identified structurally. Under simulated gastric conditions, nitrosation generally occurred only at pH values below 4.0. (63 Refs) (In GER)

61. EXPERIMENTAL INDUCTION OF IRREVERSIBLE PRECANCEROUS CHANGES IN THE PALATAL EPITHELIUM OF THE RAT.

Svensson S, Heyden G

Dept. Oral Pathology, Odontologiska Kliniken, Box 33070, S-400 33 Goteborg, Sweden

Int J Oral Surg; 11(1):52-58 1982

The spontaneous changes in the palatal epithelium following the application of 4-nitroquinoline-N-oxide (4-NQO) were studied in female Sprague-Dawley rats. 4-NQ0 was applied to the palatal mucosa (3x/wk, for 1-22 wk). In the animals subjected to 4-NQO applications for 1-10 wk, biopsies were performed 1, 15, 30, and 45 wk after the last application. In animals treated for greater than 10 wk, the first biopsy was taken 3-4 days after the last application. During the application and expectancy periods, the animals showed only a slight thickening and increased opacity of the oral mucosa. The expectancy period for the rats subjected to 1-10-wk applications of 4-NQO was 37-80 wk, compared with 8-21-wk expectancy period in the rats subjected to greater than 10-wk applications. The histological changes observed at the end of the expectancy period included slight and moderate hyperplasia and dysplasia, carcinoma in situ, and invasive carcinoma. These findings indicated that the dysplasia consistently preceded the development of invasive carcinoma in the palatal mucosa of rats and that the irreversible malignant changes in the epithelium exposed to carcinogen were already present at the stage of hyperplasia. (9 Refs)

62. DEACETYLATION OF 4-(5-ACETYLAMINO-2-FURYL)THIAZOLE TO 1-(4-THIAZOLYL)-3-CYANO-1-PROPANONE BY RAT LIVER TISSUES (MEETING ABSTRACT).

Swaminathan S, Bryan GT

Department of Human Oncology, University of Wisconsin Center for Health Sciences, Madison, WI, 53792

Proc Am Assoc Cancer Res; 23:334 1982

We postulate metabolic reduction of the rat carcinogen 4-(5-nitro-2-furyl)thiazole (NFT) to 1-(4-thiazolyl)-3-cyano-1-propanone (TCP). This may proceed from the nitro to the amino analog through the nitroso and N-hydroxylamino intermediates. Formation of TCP could occur at the stages of either N-hydroxylamino or amino intermediates by furan ring cleavage. To examine if 4-(5-amino-2-furyl)thiazole is a precursor for TCP, a stable model compound, 4-(5-acetylamino-2-furyl)thiazole (AAFT), was synthesized and its chemical identity established by spectroscopic and mass spectral analysis. Incubation with rat liver 10,000 g supernatant preparations resulted in the biotransformation of AAFT as evidenced by a decrease in absorption at 290 nm. Incubation of 14C-labeled AAFT followed by extraction with chloroform:ether (1:1) resulted in the recovery of a major portion (56%) of the radioactivity in the organic phase when the label was at the 2-position of the thiazole ring, while the major amount (82%) of radioactivity was recovered in the aqueous phase when the 1-14C-acetyl group was labeled. The radioactivity from the aqueous phase was extractable into the organic phase following acidification to pH 1, an observation consistent with deacetylation. Furthermore, the deacetylation product exhibited a mass spectrum, and retention times in gas and high pressure liquid chromatography, similar to that of synthetic TCP. (no Refs)

63. EFFECT OF THE DRUGS METHAPYRILENE AND NAFENOPIN ON CARCINOGEN-INDUCED ALTERED FOCI IN RAT LIVER (MEETING ABSTRACT).

Furuya K, Furukawa K, Mori H, Williams GM, Levine W

Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Proc Am Assoc Cancer Res; 23:400 1982

Methapyrilene, an antihistimine and nafenopin, a hypolipidemic agent, have produced liver tumors in rodents, but have shown no evidence of genotoxicity. To determine if these drugs could act as liver tumor promoters, they were fed at 0.05 and 0.1% to F344 rats for up to 24 weeks after the induction of hepatic altered foci by feeding of 0.02% N-2-fluorenylacetamide (FAA) for 8 weeks. The effect of the drugs on FAA-induced altered foci identified by resistance to iron accumulation (IR) and gamma-glutamyl transpeptidase (GGT) activity was compared to that of the liver tumor promoter phenobarbital which enhances the progression of foci to neoplasms. Like phenobarbital, methapyrilene at 0.1% increased the numbers of both IR and GGT-positive foci (6x and 3x respectively) and neoplastic nodules (10x), but not carcinomas, relative to rats returned to the control diet. Nafenopin at 0.1% decreased the numbers of GGT-positive foci by more than 0.3 although IR foci were almost the same as in controls. The number of neoplastic nodules was also reduced by more than 0.5 in the nafenopin group. Thus, methapyrilene like phenobarbital displayed a substantial enhancing effect on hepatocarcinogenesis following FAA while nafenopin was inhibitory. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

64. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: THE RUBBER INDUSTRY.

IARC Working Group
Div. Environmental Carcinogenesis, International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum 28: 486 pp., 1982.

The carcinogenic risks of exposures to workers in the rubber industry is evaluated. Manufacturing of tires, and other rubber goods are considered with respect to exposures incident to the mixing of elastomers with chemicals and their subsequent conversion into finished products. An historical overview is presented with discussion of the origins of the rubber industry and the developing rubber industry and its occupational health hazards. Manufacturing processes are described for tires, tubes, remolds, and retreads; general rubber goods such as wire and cables, belting, hose, ebonite, rubber footwear, food processing equipment, aircraft deicing equipment, automobile parts; proofed rubber fabrics, adhesives and sealants; and dipped latex products and forms. The chemistry of rubber compounding is reviewed. Exposures in the workplace are discussed with respect to controls, protective equipment, work practices; studies of exposures in the workplace; and biological monitoring. Biological effects include carcinogenic, mutagenic, and teratogenic effects of exposure to accelerators, antioxidants, curing agents; solvents; monomers; talc; carbon blacks; aromatic amines; mineral oils, tar products and polycyclic aromatic hydrocarbons; nitroso compounds; phthalate and adipate esters; and curing fumes and other emissions. Effects in humans other than cancer including dermatologic respiratory, and reproductive, are discussed. Epidemiological studies of carcinogenicity in humans are reviewed: definite associations with cancer of the urinary bladder, lymphatics, stomach, lung, and perhaps, other sites, have been made. (367 Refs)

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Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
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RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
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DIETARY FACTORS IN CARCINOGENESIS

5. ALCOHOL AND CARCINOGENESIS.
Seitz HK, Czygan P, Kommerell B
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6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
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10. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.
Madsen ES, Nielsen PA, Pedersen JC
(c/o Nielsen), Stigardsvej 2, DK-2900 Hellerup, Denmark
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12. INHALATION CARCINOGENESIS: AN OVERVIEW.
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14. ONCOGENES OF SPONTANEOUS AND CHEMICALLY INDUCED TUMORS.
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17. HYDROGEN ION DYNAMICS AND CANCER: AN APPRAISAL.
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20. HYPERPLASTIC AND NEOPLASTIC ERYTHROPROLIFERATIVE DISEASES INDUCED BY ONCOGENIC MURINE RETROVIRUSES.
Scolnick EM
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Biochim Biophys Acta; 651(4):273-283 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.
Perera FP, Weinstein IB
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Sivak A
(c/o P. H. Lohman) Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
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23. DNA REPAIR ASSAYS AS TESTS FOR ENVIRONMENTAL MUTAGENS. A REPORT OF THE U.S. EPA GENE-TOX PROGRAM.
Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
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Dept. Preventive Medicine and Community Health, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
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